University of Alberta

The Impact of Older Maternal Age on the Risk of Spontaneous Preterm Labour: A Population-Based Study in Northern and Central Alberta

by

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Abstract

The purpose of this study was to determine if older maternal age (≥ 35 years) at first birth was an independent risk factor for spontaneous preterm labour, or a risk marker exerting its influence through age-dependent risk factors. A retrospective population-based cohort study was conducted using provincial perinatal data. The study population consisted of (*N* = 193,575) nulliparous Alberta women who delivered a live born, singleton infant between 1996 and 2004.

Separate risk models for low and high risk women were developed using multivariate logistic regression. Older maternal age exerted a direct and independent effect on spontaneous preterm labour for both low risk (AOR = 1.71, 95% CI = 1.19-2.46) and high risk (AOR = 1.49, 95% CI = 1.12-1.99) nulliparous women. Older maternal age increased the risk of spontaneous preterm labour regardless of whether nulliparous women remained healthy throughout pregnancy (low risk) or whether they developed pregnancy complications (high risk).

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TABLE OF CONTENTS

CHAPTER 1 – INTRODUCTION.. 1

Statement of the Problem 1

Trends in Delayed Childbearing 4

Etiologic Heterogeneity of Preterm Birth..................................... 7

Purpose of the Study.. 10

Study Objectives.. 10

Significance of the Study 11

CHAPTER 2 – LITERATURE REVIEW 15

Selecting the Studies for Inclusion in the Literature Review.................. 17

Older Maternal Age and its Association with Spontaneous Preterm Labour 19

Heterogeneity of Preterm Birth 27

Age-Dependent Confounders 29

Summary 31

CHAPTER 3 – METHODS 40

Study Design 40

Study Objectives 40

Study Subjects 40

Data Source.. 42

Study Variables 43

Data Analysis 48

Ethical Considerations 57

CHAPTER 4 – RESULTS...58

Study Population...59

Maternal Characteristics of Low Risk Nulliparous Women..................60

Prevalence of Maternal Characteristics for Low Risk Nulliparous Women who had a Preterm or Term Birth Following Spontaneous Labour...............61

Logistic Regression Analysis for Low Risk Nulliparous Women.............62

Maternal Characteristics and Reproductive Factors for High Risk Nulliparous Women...63

Prevalence of Maternal Characteristics and Reproductive Factors for High Risk Nulliparous Women who had a Preterm or Term Birth Following Spontaneous Labour....64
Logistic Regression Analysis for High Risk Nulliparous Women.... 65
Summary of Major Findings....68
CHAPTER 5 – DISCUSSION....83
Study Strengths and Limitations....89
Implications for Nursing 93
Implications for Future Research....94
Conclusion.... 96
REFERENCES.... 98

LIST OF TABLES

Table 1 Characteristics and Results of the Studies Examining the Effect of Older Maternal Age on the Risk of Spontaneous Preterm Labour... 35

Table 2 Risk Factors Included in the Study 46

Table 3 Maternal Characteristics for Preterm and Term Births Following Spontaneous Labour in Low Risk Nulliparous Women.................. 71

Table 4 Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Predictors of Spontaneous Preterm Labour in Low Risk Nulliparous Women 73

Table 5 Maternal Characteristics and Reproductive Factors for Preterm and Term Births Following Spontaneous Labour in High Risk Nulliparous Women.. 75

Table 6 Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Predictors of Spontaneous Preterm Labour in High Risk Nulliparous Women 79

LIST OF FIGURES

Figure 1 Model 1 (Low Risk Nulliparous Women): Order of Entry of Variables into the Logistic Regression Model 54

Figure 2 Model 2 (High Risk Nulliparous Women): Order of Entry of Variables into the Logistic Regression Model...................................... 55

CHAPTER 1 – INTRODUCTION

Statement of the Problem

Preterm birth remains the most significant public health problem facing providers of maternal and infant care in Canada (Kramer et al., 1998; McCormick, 1985). Despite improvements in high-risk obstetrical care and neonatal medicine, efforts to manage and to prevent preterm birth have failed to reduce its incidence. Instead, the preterm birth rate has increased steadily in many high income countries including both Canada and the United States. Between 1991 and 2003, the Canadian preterm birth rate increased from 6.6% to 7.7%. Over the same period (1996 and 2003), the rate in the United States rose from 11% to 12.3% (Hamilton, Martin, & Sutton, 2004; Health Canada, 2003; Statistics Canada, 2005; Statistics Canada, 2006d; Ventura, Martin, Curtin, & Mathews, 1999). The rise in preterm birth rates has been linked to a number of factors including advanced maternal age at first birth, the use of assisted reproductive technology (ART) and/or ovulation induction, increasing rates of multiple births, changes in the registration of infants weighing < 500g, and improvements in obstetrical interventions that have resulted in gestational age and birth weight-specific declines in infant mortality and a rise in the number of infants surviving at lower limits of viability (Blondel et al., 2002; Joseph, Demissie, & Kramer, 2002; Joseph & Kramer, 1996; Joseph et al., 1998; Kramer et al., 1998; Tough et al., 2002).

The increasing preterm birth rate is of great concern to health professionals and policy-makers due to its association with increased mortality and morbidity that persists throughout the life span. Although preterm births account for only 5 to 12% of all live births in Canada, they are associated with 60-80% of infant deaths, and approximately 50% of cognitive delays and learning disabilities (Health Canada, 2003; Moutquin & Papiernik, 1990). Neurodevelopmental handicaps, such as cerebral palsy, seizure disorders, mental disorders, and delays in psychomotor development, are more likely to occur in infants born preterm (Brown, 1993; Knoches & Doyle, 1993; Paneth, 1995; Stoelhorst et al., 2003). These disorders are related to the complications of prematurity, including perinatal asphyxia, bronchopulmonary dysplasia, respiratory distress syndrome, and intraventricular hemorrhage (Brown, 1993; Knoches & Doyle, 1993).

The medical impact of preterm birth also places an enormous psychological and economic burden on parents, caregivers, and society in general (Petrou, Sach, & Davidson, 2001). In 1995, it was conservatively estimated that for every preterm low birth weight infant born in Canada, neonatal intensive care and post-neonatal care up to one year of age cost approximately $48,183 per survivor (Moutquin & Lalonde, 1998). Similar findings in the United States suggest that infants born at less than 37 weeks gestation between 1989 and 1992 accounted for 57% of the total initial costs for neonatal care (St. John, Nelson, Cliver, Bishnoi, & Goldenberg, 2000). The mean costs associated with initial hospitalization ranged from $10,561 for infants born between 33 and 36 weeks gestational age to a mean of $239,749 for extremely preterm infants born at 26 and 28 weeks (Cuevas, Silver, Brooten, Youngblut, & Bobo, 2005). Over time, preterm infants are more likely to be re-hospitalized within the first two years of life, experience chronic conditions requiring ongoing medical care, and need special education and social services well into later childhood (Lewit, Baker, Corman, & Shiono, 1995; Petrou et al., 2003; Petrou et al., 2001; Tommiska, Tuominen, & Fellman, 2003). The health care costs associated with caring for all surviving preterm birth infants with permanent chronic conditions have been estimated to be more than 8 billion dollars over a lifetime (i.e., 72 years) (Moutquin & Lalonde, 1998). Canadian researchers have suggested that these health care costs could be reduced by 2 billion dollars per year if the preterm birth rate could be decreased by 20% through prevention efforts (Moutquin & Lalonde, 1998); an important consideration in the current era of fiscal restraint and limited health care resources.

There have been numerous studies where the focus was the etiology of preterm birth. In these studies, researchers were able to demonstrate that preterm birth is a multi-factorial and heterogeneous outcome (Ananth, Joseph, Oyelese, Demissie, & Vintzileos, 2005), resulting from the interaction of demographic, biomedical, psychological and behavioural/lifestyle risk factors. After completing extensive literature reviews, some authors were able to identify variables with well-established causal effects (Berkowitz & Papiernik, 1993; Kramer, 1987). However, much of the etiology of prematurity remains unexplained.

Unfortunately, many of the identified risk factors for preterm birth are not modifiable, and therefore cannot be targeted for reduction by prevention programs. However, one potentially modifiable risk factor is maternal age at first birth. With appropriate health counseling from professionals on the risks of delayed childbearing, women will be able to make informed choices about when to start a family.

Researchers have shown that older maternal age (defined as age 35 years and older at time of delivery) is associated with sub-fertility, chromosomal abnormalities, and multiple gestation (Cleary-Goldman et al., 2005; Cnattinguis, Forman, Berendes, & Isotalo, 1992; Edge & Laros, 1993; Scholz, Hass, & Petru, 1999). Furthermore, some researchers have found an association between older maternal age and preterm birth (Astolfi & Zonata, 1999; Mohsin, Wong, Bauman, & Bai, 2003; Verkerk, Zaadstra, Reerink, Herngreen, & Verloove-Vanhorick, 1994; Wen, Goldenberg, Cutter, Hoffman, & Cliver, 1990). Other researchers have challenged these findings (Barkan & Bracken, 1987; Beydoun et al., 2004; Kolas, Nakling, & Salvesen, 2000; Malloy, 1999).

More women are delaying childbirth into their mid-thirties and later. Therefore, health care providers need current conclusive research findings regarding the impact of older maternal age on the risk of preterm birth so that they can provide appropriate pre-conceptual and antenatal counseling.

Trends in Delayed Childbearing

Older maternal age is becoming increasingly common. Since the 1970s there has been a rise in the number of Canadian women postponing the birth of their first child. Between 1974 and 1994, the proportion of first live births delivered by women aged 35 to 39 years rose from 13% to 25% (Ford & Nault, 1996). By 2003, this percentage increased to 28.1% (Statistics Canada, 2006b). Similarly, 2.6 % of all live births in 2003 were delivered by women aged 40 to 44 years (up from 1.1% 10 years earlier) (Health Canada, 2003; Statistics Canada, 2006c). Of these births, 26.3% were first births, an increase of 3.7% between 1991 and 2003 (Statistics Canada, 2005; Statistics Canada, 2006b). In Alberta, the mean maternal age at first birth increased steadily from 26 to 27 years of age between 1992 and 2002 (Reproductive Health Report Working Group, 2004).

Similar trends have been reported in other industrialized countries. For example, approximately 40% of all live births in the United States are first births, with women 30 years of age and older accounting for 25.8% of these births in 2003, up from 22.5% in 1997 (Hamilton et al., 2004; Ventura et al., 1999). The United States also reported a birth rate increase of 31% for women aged 35 to 39 years and 51% for women aged 40 to 44 years between 1990 and 2002 (Martin et al., 2003). In 2002, the mean age of women having their first child reached 25.1 years, an all-time high, while the birth rate declined for women 15 to 24 years of age (Martin et al., 2003).

Demographic trends in Canada and the United States suggest that there are a number of socioeconomic changes contributing to women delaying childbirth. More women are now pursuing higher education and advancing their careers, while at the same time postponing marriage to achieve these goals. For example, the number of Canadian women aged 25 to 44 years with a university degree increased from 689,900 to 1,307,100 between 1990 and 2005 (Statistics Canada, 2006a). This increase corresponds to a rise in the age-specific first marriage ratios between 1992 and 2002 among women aged 35 to 39 years (4.3 per 1,000 females to 6.2 per 1,000 females) and women aged 40 to 44 years (1.6 per 1,000 females to 2.4 per 1,000 females) (Statistics Canada, 2003; Statistics Canada, 2006e). In addition, by 1994, almost half of the first births to American females were to women with 16 or more years of education (Heck, Schoendorf, Ventura, & Kiely, 1997). The availability of birth control, second marriages, the need for dual incomes (Freeman-Wang & Beski, 2002; Newburn-Cook & Onyskiw, 2005), and a history of infertility (Kessler, Lancet, Borenstein, & Steinmetz, 1980) have also been cited as other factors contributing to the postponement of childbirth.

Unfortunately, the longer women delay starting a family, the more fertility concerns may arise. Decreasing fertility and fecundity in women over the age of 35 years has been well documented (Berendes & Forman, 1991; Gosden & Rutherford, 1995; Hansen, 1986). Reasons for this biological outcome include poor ovulatory function, poor oocyte quality, an increase of genetic anomalies in oocytes and embryos, and a decreased rate of embryo implantation (Bowman & Saunders, 1995; Pal & Santoro, 2003).

Difficulty conceiving has led to the increased use of assisted reproductive technologies (ART) and/or ovulation induction. As a result, an associated rise in the number of multiple gestations has been documented and linked to both older maternal age at first birth and to increased rates of preterm birth (Luke & Martin, 2004). Canadian researchers reported that Alberta women having children at age 35 years and older (excluding in vitro fertilization pregnancies) accounted for a 23% increase in the multiple birth rate (Tough et al., 2002). Delayed childbearing in this population was also associated with a 40% increased risk of delivering a preterm baby (Tough et al., 2002).

Etiologic Heterogeneity of Preterm Birth

Although some researchers have shown that there is an increased risk of preterm birth with older maternal age (Astolfi & Zonata, 1999; de Sanjose & Roman, 1991; Mohsin, Wong, Bauman, & Bai, 2003; Verkerk, Zaadstra, Reerink, Herngreen, & Verloove-Vanhorick, 1994; Wen, Goldenberg, Cutter, Hoffman, & Cliver, 1990), other researchers have demonstrated no increased risk (Arbuckle & Sherman, 1989; Barkan & Bracken, 1987; Kolas, Nakling, & Salvesen, 2000; Nordentoft et al., 1996; White, 2004). These equivocal findings may be due to a number of methodological differences and limitations present across the various studies, such as inconsistencies in defining what constitutes older maternal age, inadequate control for potential risk factors and age-dependent covariates, inadequate sample sizes (reduced study power), differences in the age category selected for reference group comparisons, the use of hospital-based versus population-based samples, and a failure to consider the heterogeneity of preterm birth itself (Berkowitz & Papiernik, 1993; Kramer, 1987; Newburn-Cook & Onyskiw, 2005). Contradictory findings have led to confusion surrounding whether older maternal age has an independent (direct) negative effect on gestational age and leads to an increased risk of preterm birth. In addition, the majority of past researchers have treated preterm birth as a single outcome (i.e., the birth of an infant < 37 weeks gestational age), which may have prevented them from "determining conclusively the relationship between older maternal age and the risk of preterm delivery" (Newburn-Cook & Onyskiw, 2005, p. 855).

Preterm births are classified into three distinct clinical presentations (or subtypes): those that arise from idiopathic preterm labour (spontaneous onset of uterine contractions with or without rupture of the chorionamniotic membranes), preterm birth following premature rupture of membranes, and medically indicated preterm birth (also referred to as iatrogenic preterm birth), which is often necessitated in the presence of fetal distress or maternal factors such as pre-eclampsia and other pregnancy complications (Savitz, Blackmore, & Thorp, 1991). Some authors who oppose the separation of preterm births into these subtypes make the theoretical argument that these subtypes may not reflect etiologically different entities, but rather result from differences in the timing of diagnosis and access to medical care (Klebanoff, 1998; Klebanoff & Shiono, 1995). These authors suggest that there may be substantial etiologic overlap between preterm birth caused by spontaneous preterm labour or premature rupture of membranes, thereby making the separation of these categories difficult. Moreover, they argue that there is etiologic overlap between spontaneous preterm births and medically indicated preterm births, stating that in the absence of medical intervention many of these births would have occurred spontaneously due to underlying medical causes. While some researchers have shown there is etiologic overlap among the preterm birth subtypes (Moutquin, 2003; Pickett, Abrams, & Selvin, 2000; Savitz et al., 2005), other researchers have demonstrated that distinct causal factors leading to the different subtypes may exist

(Berkowitz, Blackmore-Prince, Lapinski, & Savitz, 1998; Harlow et al., 1996; Kristensen, Langhoff-Roos, & Kristensen, 1995; Meis et al., 1995; Pickett et al., 2000).

Overall, researchers suggest that relatively little attention has been given to the possibility that different causal mechanisms can lead to different prematurity outcomes (Savitz et al., 1991). They also note that the etiology of preterm birth following spontaneous onset of labour is poorly understood even though it is a significant contributor to all preterm births (Savitz et al., 1991). Moreover, each preterm birth subtype may not respond to the same prevention activities (Goffinet, 2005). Only a limited number of researchers have examined the determinants of spontaneous preterm labour (Table 1). Their studies will be discussed in Chapter 2.

Researchers should consider the heterogeneity of preterm birth so that the different causal mechanisms for each subtype can be identified. In addition, researchers need to consider simultaneously multiple potential risk factors in order to understand how they interact and whether they act independently or indirectly (mediated through other factors) to influence gestational age at birth.

It will be difficult to reduce the incidence of preterm birth without acting on the causes (Goffinet, 2005). Identifying the modifiable factors early in the pregnancy, or even before pregnancy, will help to enable more effective preventive measures to be taken (Robinson, Regan, & Norwitz, 2001), and thus help to reduce the preterm birth rate.

With the increasing number of women delaying childbirth into their mid-thirties and older, and the concurrent rise in preterm birth rates, the question of whether older maternal age increases the risk of preterm birth needs to be addressed. Furthermore, given the heterogeneity of preterm birth, the impact of older maternal age on each preterm birth subtype must be assessed. Women need to be assured that health care professionals have the correct information regarding the risks associated with older maternal age and adverse birth outcomes, so that they too can become aware of any potential adverse outcomes and make an informed decision about when to begin their family.

Purpose of the Study

The overall purpose of this study was to determine the impact of older maternal age on the risk of spontaneous preterm labour (spontaneous labour leading to delivery at < 37 completed weeks gestation that is not associated with either ruptured membranes or iatrogenic intervention as defined by Ananth et al., 2005) among nulliparous women.

Study Objectives

The specific objectives of this study were: 1) to determine if older maternal age at first birth (≥ 35 years of age at time of delivery) was an independent risk factor for spontaneous preterm labour or a risk marker that exerted its influence indirectly through other age-dependent risk factors (e.g., medical problems during pregnancy such as gestational diabetes, and pregnancy complications such as pregnancy-induced hypertension); and, 2) to establish separate risk models for healthy low risk nulliparous women (i.e., had no pre-existing chronic illnesses and did not develop pregnancy complications) and healthy high risk nulliparous women (i.e., had no pre-existing chronic illnesses, but developed one or more pregnancy complications).

Significance of the Study

An epidemiological framework and a population health approach guided the development and implementation of this research study. These two approaches are complementary, both seeking to identify the many determinants that influence health among women of childbearing age, including the effect of older maternal age on gestational age at the time of birth and the occurrence of spontaneous preterm labour. This information can then be used to control or prevent preterm birth.

Originally focused on the etiological determinants of disease, the focus of epidemiology has evolved to include investigating the distribution and determinants of health and illness in individuals and populations (Brunt & Shields, 2000; Gordis, 2000; Mackenbach, 1995; Valanis, 1999). Epidemiologic methods are becoming increasingly important to health care providers, including nurses, as health system priorities have changed, and are now focused primarily on primary prevention ("upstream thinking") rather than on treatment/cure of illness (Brunt & Shields, 2000).

Factors outside of the health care system identified as being influential to the health of individuals and populations are known as the "determinants of health". These health determinants include income and social status; social support; education; physical, social and work environments; biology and genetics; personal health practices and coping skills; gender; culture; health services; and healthy child development (Federal, Provincial and Territorial Advisory Committee on Population Health, 1994; Health Canada, 1996).

Similar to epidemiology, a population health approach is concerned with the determinants of health in populations, specifically the interaction among individual and collective factors and conditions contributing to the health and well being of populations (Health Canada, 1996). To effectively influence population health a better understanding of these health determinants and the complex interactions among them needs to be addressed (Federal, Provincial and Territorial Advisory Committee on Population Health, 1994).

Understanding the determinants of health is important for primary prevention. However, the role of nurses in the identification of these determinants is still in its infancy. Butterfield (2002) noted that, "with few exceptions, nursing has not been active in efforts to understand the etiology of disease" (p. 33). She believes that nurses have an important role in advancing "upstream thinking" through research efforts that address the determinants of diseases impacting their clients. Nurses are in a key position to influence birth outcomes due to their contact with families before, during and after pregnancy. Consequently, they need to understand what factors are involved, and how these factors interact to influence pregnancy outcomes, including gestational duration.

The results of this study will provide further insight into the determinants of spontaneous preterm labour in Northern and Central Alberta and in particular, whether or not pregnancy in nulliparous women who are ≥ 35 years of age is associated with an increased risk of spontaneous preterm labour. As stated by the World Health Organization (2002), focusing on the risks to health is important to prevention and requires examining both proximal and distal causes of adverse health outcomes because risks do not occur in isolation (Misra, O'Campo, & Strobino, 2001; Myslobodsky, 2001). Examining the direct and indirect effects of biological, genetic, lifestyle, and socio demographic variables, including maternal age, will increase understanding of how these factors work together to influence gestational age at birth. Furthermore, identifying any modifiable risk factors, such as maternal age, and their impact on pregnancy outcomes, can be used to develop interventions and/or prevention programs.

With more women delaying the birth of their first child until 35 years of age and beyond, and with the preterm birth rate on the rise, nurses need to know whether older maternal age (a potentially modifiable risk factor) has an independent/direct effect or interacts with other factors to increase the likelihood of spontaneous preterm labour. This information is needed by health care providers in the provision of pre-conceptual and antenatal counseling, as well as by women who are deciding about when to begin their families. The knowledge gained from this study will help nurses to develop effective primary prevention interventions or programs aimed at reducing modifiable risk factors that shorten gestational duration. In addition, nurses will be better equipped to work with health care policy-makers to create and implement health-oriented public policy targeted towards improving maternal, fetal and newborn health and hence population health (Glass & Hicks, 2000; White, 2004). These actions will promote the health of childbearing women and possibly lead to better birth outcomes.

CHAPTER 2 – LITERATURE REVIEW

Concern over the potential risks of older maternal age on birth outcomes arose over 3 decades ago (early 1970s) when the International Federation of Obstetrics and Gynecologists (IFOG) classified women who delivered their first child at age 35 or older as "elderly primigravidae" (Cunningham & Leveno, 1995; Kirz, Dorchester, & Freeman, 1985). Since then, there have been numerous researchers investigating the effect of older maternal age (≥ 35 years of age at time of delivery) on various maternal and fetal outcomes, including the risk of preterm birth. Unfortunately, the results of these studies have been inconclusive and sometimes contradictory. For example, several researchers have found an association between older maternal age and the risk of preterm birth (Alexander, Baruffi, Mor, & Kieffer, 1992; Astolfi & Zonata, 1999; de Sanjose & Roman, 1991; Ekwo & Moawad, 2000; Mohsin, Wong, Bauman, & Bai, 2003; Mor, Alexander, Kogan, Kieffer, & Ichiho, 1995; Newburn-Cook et al., 2002; Tough, Svenson, Johnston, & Schopflocher, 2001; Verkerk, Zaadstra, Reerink, Herngree, & Verloove-Vanhorick, 1994; Wen, Goldenberg, Cutter, Hoffman, & Cliver, 1990). However, other researchers have not supported this finding. They have concluded that older maternal age does not increase the risk of preterm birth (Arbuckle & Sherman, 1989; Barkan & Bracken, 1987; Beydoun et al., 2004; Frisbie, Biegler, de Turk, Forbes, & Pullum, 1997; Kolas, Nakling, & Salvesen, 2000; Mvula & Miller, 1998; Nordentoft et al., 1996; Shiono & Klebanoff, 1986; Shults, Arndt, Olshan, Martin, & Royce, 1999; Virji & Cottington, 1991; White, 2004).

As discussed in Chapter 1, the disparate findings reported in past studies may be due to methodological limitations and study differences. These include inadequate sample sizes and lack of study power; differences in the study setting and population sampled (i.e., population-based versus hospital-based studies); inadequate control of age-dependent confounders that are also associated with pregnancy outcomes; failure to consider the relationship between maternal age and pre-existing chronic diseases and pregnancy complications that are associated with older maternal age; inconsistency in the definition of what constitutes older maternal age and choice of the specific reference age group for comparisons; differences in data sources used, resulting in incomplete and/or inaccurate data on risk factors; and varying definitions of birth outcomes being assessed (Berkowitz & Papiernik, 1993; Kramer, 1987; Newburn-Cook & Onyskiw, 2005). In addition, the equivocal results may be due to the fact that the majority of the researchers have treated preterm birth as a single entity or homogeneous birth outcome without acknowledging that preterm birth is a "cluster of conditions with different etiologies" or different etiological pathways (Pickett et al., 2000, p. 305).

The impact of maternal age on the incidence of preterm birth may in fact vary as a function of the specific preterm birth subtype (i.e., preterm birth following spontaneous labour, preterm birth following ruptured membranes, or medically indicated preterm birth) (Savitz et al., 1991). Failing to consider the heterogeneity of preterm birth may prevent the identification of any differential age effects for each subtype.

The purpose of this literature review is to identify, select and examine the results of studies where researchers have estimated the impact of older maternal age on two preterm birth subtypes (i.e., preterm birth following ruptured membranes or preterm birth following spontaneous labour) or preterm birth with or without ruptured membranes (i.e., PT-both). This review will include a critique of both the strengths and weaknesses of the studies selected.

Selecting the Studies for Inclusion in the Literature Review

The present literature review extends the work of Newburn-Cook and Onyskiw (2005). These researchers conducted a systematic review of the literature (1985 to 2002) to examine the impact of advancing maternal age on spontaneous preterm birth and fetal growth restriction. Studies were selected by these researchers if they met the following inclusion criteria: 1) assessed risk factors for preterm birth by subtype (i.e., idiopathic preterm labour, preterm premature rupture of membranes) and small-for-gestational age birth (fetal growth restriction); 2) used acceptable definitions of these birth outcomes; 3) were restricted to singleton live births; 4) were conducted in a developed country; and, 5) were published in English. The same criteria were used in retrieving and selecting the literature included in this review.

A comprehensive search for additional published and unpublished studies for the period January 2003 to July 2005 was undertaken using a number of search strategies. These included a computerized search of various online databases (i.e., MEDLINE, CINAHL, EMBASE, HEALTHSTAR, Web of Science, ABI Inform, Academic Search Premier, Sociological Abstracts), abstracting services (i.e., Proquest

Dissertations & Theses), and the Cochrane Collaboration Database. The medical subject headings (MeSH) and keywords used to locate and retrieve articles were: *older maternal age*, *maternal age*, *maternal age 35 and over*, *advanced maternal age*, *spontaneous preterm labor*, *spontaneous preterm delivery*, *premature rupture of membranes*, *preterm birth subtypes*, *preterm delivery subtypes*, *preterm birth*, *low birth weight*, *risk factors*, *pregnancy complications*, *pregnancy outcome*, and a combination of these terms. In addition to the online searches, reference lists of pertinent studies were examined for other potentially relevant articles.

Articles were screened for any words in the title or abstract that indicated an investigation into the risk factors for preterm birth. Studies where the focus was primarily on other risk factors were considered for review if the researchers provided a risk estimate of older maternal age on preterm birth. The majority of articles included in this review had risk factors other than maternal age as the primary focus (e.g., nutrition, various clinical and obstetric risk factors). For example, Berkowitz and her colleagues (1998) assessed simultaneously the effect of previously identified sociodemographic, obstetric, nutritional, and medical risk factors on preterm birth due to spontaneous labour, premature rupture of membranes or medical indications. Because older maternal age was included in the analysis, this investigation met the inclusion criteria outlined by Newburn-Cook and Onyskiw (2005), and was included in this review, along with studies that considered maternal age as the independent variable of interest.

Approximately 50 articles were retrieved, but only one study by Heaman, Blanchard, Gupton, Moffatt, and Currie (2005) met the criteria established by Newburn-Cook and Onyskiw (2005). This study was added to those investigations previously selected by these authors. The characteristics and results of the eight studies included in this literature review are summarized in Table 1 on page 35.

Older Maternal Age and its Association with Spontaneous Preterm Labour

All of the studies included in this review had at least two preterm birth subtypes as the dependent variable (Aldous & Edmonson, 1993; Berkowitz, 1985; Berkowitz et al., 1998; Harlow et al., 1996; Heaman et al., 2005; Kramer, McLean, Eason, & Usher, 1992; Lang, Lieberman, & Cohen, 1996; Mercer et al., 1996). In six of these studies, the researchers grouped preterm birth due to spontaneous (idiopathic) labour or preterm premature rupture of membranes into a single birth outcome (Aldous & Edmonson, 1993; Berkowitz, 1985; Heaman et al., 2005; Kramer et al., 1992; Lang et al., 1996; Mercer et al., 1996), which will be referred to as PT-both for the purposes of this review. The remaining researchers conducted separate analyses for preterm birth due to spontaneous labour, preterm premature rupture of membranes, or preterm births that were medically indicated (Berkowitz et al, 1998; Harlow et al., 1996).

While the majority of the authors equated preterm birth to a preterm delivery preceded by preterm premature rupture of membranes or spontaneous labour (PT-both), Kramer et al. (1992) used a different definition that concurred with the theoretical argument of Klebanoff and Shiono (1995). Klebanoff and Shiono argued that "a non-trivial fraction of 'elective' preterm births would have been 'spontaneous' had the managing clinician not intervened" (p. 126). Based on this argument, Kramer et al. controlled for any preterm births not considered spontaneous or potentially spontaneous by including only those preterm births occurring from spontaneous labour, from inductions for preterm premature rupture of membranes or chorioamnionitis, or from cesarean sections due to maternal or fetal indications (e.g., abruptio placentae, placenta previa). Kramer et al. excluded preterm births following induced labour or a cesarean section for which there was no medical threat. These researchers acknowledged that any discrepancies between their results and the findings in other studies could be due to the inclusion of induced preterm deliveries in their analyses. Because Kramer and his colleagues defined preterm birth (PT-both) differently, caution should be taken when comparing their results with the findings of the other studies included in this review.

The studies varied with respect to study design, sample size and data sources used to obtain the potential risk factors (including maternal age) and birth outcomes. In six studies, researchers used a cohort study design (Aldous & Edmonson, 1993; Berkowitz et al., 1998; Harlow et al., 1996; Kramer et al., 1992; Lang et al., 1996; Mercer et al., 1996), while in the other two studies, researchers conducted case-control investigations (Berkowitz, 1985; Heaman et al., 2005). All but three studies had hospital-based samples and included study data gathered from administrative databases, interviews and medical records (Berkowitz, 1985; Berkowitz et al., 1998; Heaman et al., 2005; Kramer et al., 1992; Lang et al., 1996). Two of the cohort studies were prospective and were restricted to women participating in larger research projects (i.e., RADIUS and the Preterm Birth Prediction Study, respectively) (Harlow et al., 1996; Mercer et al., 1996). Women in these studies were followed prenatally through to delivery with data being collected prior to delivery via interview (e.g., demographic information, lifestyle choices). The remaining study by Aldous and Edmonson (1993) was the only population-based study. These investigators used birth certificates to acquire information on all white and black infants born in Washington State between 1984 and 1988.

Due to the differences in how samples and data were acquired, the number of subjects varied among the studies. Sample sizes ranged from 488 to 31,107 births. A small sample size present in three studies may have prevented an adequate examination of the impact that older maternal age had on PT-both (Berkowitz, 1985; Heaman et al., 2005; Mercer et al., 1996). In two of these studies, researchers excluded older maternal age from the final regression model when it proved to be insignificant in the univariate analysis (Heaman et al., 2005; Mercer et al., 1996). In the other study, the investigator found that older maternal age was insignificant in the multivariate analysis (no odds ratio was reported) (Berkowitz, 1985). These studies may have been under-powered because of their limited sample sizes. For example, Berkowitz (1985) recruited only 488 participants (175 cases and 313 controls) who delivered at Yale-New Haven Hospital to assess various clinical and obstetric risk factors for PT-both. However, as Berkowitz points out, the sample size may have been insufficient to properly assess the independent effects of variables entered simultaneously into the multivariate model.

Similarly, Heaman et al. (2005) modeled several sociodemographic, behavioural, psychosocial, and biomedical risk factors for PT-both for both Aboriginal and non-Aboriginal women. The subjects in this study consisted of 226 preterm infants (82 Aboriginal) and 458 term infants (176 Aboriginal) born at two tertiary care hospitals. Through multivariate analysis, they found young maternal age (< 19 years of age; AOR = 0.19, 95% CI = 0.04-0.89) to be a protective factor for Aboriginal women, a finding that was contrary to the results for non-Aboriginal women. However, these results may be questionable given the small sample size. Heaman et al. concluded that there were insufficient numbers of subjects for adequate racial/ethnic stratification. Therefore, this study was an exploratory study, and as such, did not provide definitive findings for the determinants of PT-both in Aboriginal and non-Aboriginal Canadian women.

Mercer et al. (1996) were at the same disadvantage with only 1,218 nulliparous and 1,711 multiparous women participating in the Preterm Birth Prediction Study to investigate the predictability of a risk assessment system for PT-both. After assessing several risk factors simultaneously, including maternal age, they reported that all the risk factors had low predictive value for PT-both in both nulliparous and multiparous women. Unfortunately, the large number of risk factors assessed, along with the small sample size used, led to tentative and inconclusive results.

Although the rest of the researchers in this review used larger samples, they had other methodological limitations present in their research that need to be considered before accepting the conclusions. Kramer et al. (1992) were the only researchers to develop separate risk models for PT-both at < 37, < 34, and < 32 completed weeks gestation. Dividing PT-both in this manner enabled Kramer and his colleagues to detect any varying effects each determinant had for moderately preterm, very preterm and extremely preterm births. Their study sample included 13,102 singleton, live born infants delivered at Montreal's Royal Victoria Hospital. Using a retrospective cohort study design, they investigated the impact of maternal nutrition and other determinants, including older maternal age, on PT-both. After controlling for age-dependent confounders (i.e., pregnancy-induced hypertension, pre-pregnancy hypertension, diabetes, education), Kramer et al. concluded that women aged 35 years and older were at no greater risk for delivering an infant at < 37 weeks gestation (AOR = 1.13, 95% CI = 0.98-1.24), < 34 weeks gestation (AOR = 1.15, 95% CI = 0.93-1.41), or < 32 weeks gestation (AOR = 1.05, 95% CI = 0.79-1.40) when compared to women 20 to 34 years of age. However, the generalizability of the study findings is limited given the use of a hospital-based sample. Moreover, as mentioned previously, Kramer and colleagues included inductions and cesarean sections in their study, unlike the other studies in this review, which makes comparing their findings to those in the other studies difficult.

Aldous and Edmonson (1993) conducted the only study where the objective was specifically to investigate the effects of older maternal age on various birth outcomes (i.e., low birth weight, very low birth weight, and PT-both). Using a population-based study, a total of 16,492 white and 4,403 black, first born, singleton, live born infants were included in their investigation. Information recorded on Washington State birth certificates was used for acquiring the risk factors included in the risk modeling and PT-both. Aldous and Edmonson grouped maternal age into five-year categories, with older maternal age being separated into women aged 35 to 39 years and ≥ 40 years of age. This was the only study that provided a separate risk estimate for women ≥ 40 years of age. By stratifying maternal age into these categories and through adequate control for age-dependent confounders (i.e., pre-existing hypertension, socioeconomic status, smoking), Aldous and Edmonson were able to establish a moderate, but progressive increased risk of PT-both with advancing maternal age. The highest risk was seen in women ≥ 40 years of age (AOR = 1.8, 95% CI = 1.3-2.6) with significant risk beginning in women aged 30 to 34 years (AOR = 1.4, 95% CI = 1.1-1.7). Although an analysis for black infants was completed, there were no significant findings. However, the small number of black infants born to women 35 years and older (*n* = 127) and the resulting imprecise risk estimates, made these findings inconclusive. Because this was the only study to demonstrate a significant association between older maternal age and PT-both, and it was the only study to have older maternal age as the independent variable, more research is needed to investigate the relationship between older maternal age and this birth outcome.

One of the methodological strengths exhibited in all the studies was the inclusion of age-dependent confounders in the analyses; these are factors associated with increasing age that have a negative impact on birth outcomes (e.g., pregnancy complications and/or pre-existing medical conditions). However, the researchers varied as to what risk factors they included, making comparison of results difficult. In order to focus on women who were healthy at the start of their pregnancies, both Harlow et al. (1996) and Lang et al. (1996) excluded women with pre-existing medical conditions, but these researchers varied as to which women they excluded. Lang and associates excluded those women with epilepsy, asthma, diabetes mellitus and hypertension, while Harlow et al. excluded those women with chronic renal disease, diabetes mellitus and hypertension. All but two of the remaining studies (Berkowitz, 1985; Heaman et al., 2005) had adjustments for chronic medical conditions in the analyses. In two of these studies, the researchers included a wide range of pregnancy complications (Lang et al., 1996; Mercer et al., 1996); the rest included as few as none to as many as three potential pregnancy complications (e.g., gestational diabetes, pregnancy induced hypertension, bleeding during pregnancy).

The studies included in this literature review also differed on how older maternal age, as well as the reference age group chosen for comparison, were defined. Despite the IFOG definition of older maternal age as being ≥ 35 years of age, only half the researchers used this definition; and, when they did, they differed on the choice of reference age group. One study included women 20 to 29 years of age as a reference group (Berkowitz et al., 1998); another included women 20 to 30 years of age (Harlow et al., 1996) as the age group for comparison. Kramer et al. (1992) and Lang et al. (1996) selected women 20 to 34 years of age and 25 to 34 years of age, respectively, as the reference age group for their analyses. Berkowitz (1985) defined older maternal age as 35 to 41 years, but did not report a reference group due to the insignificant findings between older maternal age and PT-both. In two studies where older maternal age was defined as > 35 years, women 19 to 35 years of age and 16 to 35 years of age respectively were chosen as the group for comparison (Heaman et al., 2005; Mercer et al., 1996). In the study where older maternal age was stratified into 35 to 39 years and ≥ 40 years of age, women 20 to 24 years of age were included as the reference group (Aldous & Edmonson, 1993). All the differing definitions of age make comparison of results across studies a challenge.

Overall, the studies reviewed here show that the effect of older maternal age on PT-both remains inconclusive. A lack of population-based samples, along with the use of smaller samples (in three studies) (Berkowitz, 1985; Heaman et al., 2005; Mercer et al., 1996), limits the generalizability and validity of the findings. Interestingly, the only study to find a significant association between older maternal age and PT-both was also the only population-based study in this review (Aldous & Edmonson, 1993). The discrepancy in findings between this study and the others may reflect differing sample characteristics. Several confounders were included in all the studies, but the type and number of confounders varied. Furthermore, with the exception of one study (Lang et al., 1996), there was no clear assessment of the direct or indirect effect of risk factors. More attention to the determinants of the different preterm birth subtypes that may play an intermediate role in the etiological chain is necessary to achieve clarity around the direct causes of this birth outcome.

Finally, in all studies, age definition and choice of reference age group needs more refinement if results are to be compared in the future.

Heterogeneity of Preterm Birth

Two groups of researchers in this review developed separate risk models for preterm birth due to spontaneous labour or preterm premature rupture of membranes using several previously identified risk factors (Berkowitz et al., 1998; Harlow et al., 1996). Berkowitz et al. (1998) included both high and low-risk pregnancies in their study and used a retrospective cohort design to investigate the impact of several risk factors on each preterm birth subtype (i.e., preterm birth due to spontaneous labour, preterm birth due to preterm premature rupture of membranes, or medically indicated preterm births). A hospital-based sample of 31,107 births was used. After controlling for several known risk factors, Berkowitz et al. found that both women 30 to 34 years of age (AOR = 1.4, 95% CI = 1.2-1.6) and women ≥ 35 years of age (AOR = 1.5, 95% CI = 1.3-1.8) were at greater risk for preterm birth following preterm premature rupture of membranes when compared to women 20 to 29 years of age. Older maternal age was not a significant predictor for preterm birth due to spontaneous labour.

Like Berkowitz et al. (1998), Harlow and his colleagues (1996) had a large sample (*n* = 14,948) to conduct their analysis of potential risk factors for each preterm birth subtype. However, their study sample was restricted to low-risk pregnancies (i.e., no medical indication for ultrasound at the first visit and exclusion of women with pre-existing diseases) and to participants from the RADIUS study. Unlike Berkowitz et al., Harlow and his associates were not able to clearly demonstrate their maternal age result. Harlow et al. classified maternal age as a continuous variable (maternal age per 5 years) and as a result could only describe the impact of increasing maternal age, not older maternal age. The findings showed borderline significance for maternal age and preterm premature rupture of membranes (AOR = 1.3, 95% CI = 1.0-1.5); however, these researchers concluded that maternal age "was predictive for premature rupture of membranes" (p. 446). This weak result may have been a reflection of the healthy population used to investigate their objectives. Like Berkowitz et al., Harlow and his colleagues did not find a significant association between maternal age and preterm birth due to spontaneous labour.

Both Berkowitz et al. (1998) and Harlow et al. (1996) acknowledged that distinguishing between preterm birth following preterm premature rupture of membranes or spontaneous labour could be problematic. However, the findings from both studies indicate that there may be differential effects for maternal age on each preterm birth subtype. The results reported by Berkowitz et al. show that older maternal age increases the risk of preterm birth arising from preterm premature rupture of membranes, but not spontaneous labour, while the results reported by Harlow et al. show the same findings for maternal age. Unfortunately, the investigators' use of varying definitions of older maternal age in these studies prevents the establishment of definitive conclusions.

More research is needed to examine causal factors for each preterm birth subtype. Future studies should include a population-based sample, differentiate between high and low risk women, and control for a wide range of potential confounders.

Age-Dependent Confounders

There are several researchers who have investigated the complications of pregnancy, particularly in older gravida. The overwhelming majority has shown that there is an increased risk of chronic medical conditions and pregnancy complications in women of older maternal age. In a recent US study, researchers found that certain maternal complications were positively associated with maternal age in a dose-dependent fashion (Salihu, Shumpert, Slay, Kirby, & Alexander, 2003). For example, the rate of chronic hypertension per 1000 deliveries in women 20 to 29 years of age was 5.3. This rate increased to 10.4 for women aged 30 to 39 years, to 23.8 for women aged 40 to 49 years and to 27.8 for women aged 50 and over.

The results of this study confirm previous results that established older women were more likely to be at higher risk for antepartum and intrapartum complications when compared to their younger counterparts (Berkowitz, Skovron, Lapinski, & Berkowitz, 1990; Gilbert, Nesbitt, & Danielsen, 1999; Jolly, Sebire, Harris, Robinson, & Regan, 2000; Prysak, Lorenz, & Kisly, 1995). For instance, in a population-based study in the UK, it was found that women older than 40 years of age were three times more likely to have placenta previa when compared to women 18 to 34 years of age (AOR = 3.09, 99% CI = 2.19-4.36) (Jolly et al., 2000). Similarly, it was determined that, after adjusting for race and underlying medical conditions, women 35 years of age and older were two times more likely to have antepartum complications than women 20 to 29 years of age (i.e., gestational diabetes, abruptio placentae, and placenta previa; AOR = 2.0, 95% CI = 1.6-2.5) (Berkowitz et al., 1990). Results of these studies indicate the importance of including age-dependent confounders in an analysis of older maternal age and spontaneous preterm labour so that the presence of any independent association between older maternal age and this birth outcome can be determined.

Pregnancy complications have been identified as intermediate outcomes of preterm birth (i.e., other risk factors act indirectly through these factors) (Kramer, 1987). As a result, in one study where the mediating role of pregnancy complications was examined, the researchers first assessed the effect of 23 different risk factors on PT-both without pregnancy complications in the risk model, and then assessed their effect when pregnancy complications were added (Lang et al., 1996). By proceeding in this fashion, the indirect effects of other risk factors were determined by noting any significant changes in the risk estimates. Although there was no significant change in the odds ratio for older maternal age, Lang et al. were able to identify the direct and indirect effects of other risk factors. For example, the odds ratios for low pre-pregnant weight, previous preterm birth, three or more miscarriages, two or more stillbirths, in utero DES exposure, and low weekly weight gain showed significant moderate decreases after pregnancy complications were added to the model. These results indicate that these particular risk factors may act indirectly through pregnancy complications to influence PT-both. Older maternal age was a non-significant risk factor for PT-both (AOR = 1.1, 95% CI = 0.8-1.6) regardless of whether pregnancy complications were in the risk model. Lang et al. were unique in their assessment of pregnancy complications and, as a result, were able to provide methodological direction for future studies specifically addressing the effects of older maternal age on spontaneous preterm labour.

To accurately assess the impact of older maternal age on spontaneous preterm labour, other potential confounders along with chronic medical conditions and pregnancy complications need to be considered in the risk modeling. Kramer (1987) and Berkowitz and Papiernik (1993) completed two comprehensive reviews of potential risk factors for preterm birth. These two reviews were used to determine which risk factors and covariates were included along with maternal age in the risk modeling for this study (described in chapter 3).

Summary

The results of the studies reviewed provide some evidence that there is an older maternal age effect on the incidence of PT-both (i.e., preterm birth preceded by preterm premature rupture of membranes or spontaneous labour). Other studies have shown that older maternal age is associated with an increased prevalence of chronic diseases, medical problems during pregnancy, as well as antepartum and labour complications (Berkowitz et al., 1990; Gilbert et al., 1999; Jolly et al., 2000; Prysak et al., 1995; Salihu et al., 2003). However, it is not known whether older maternal age exerts an independent and direct effect on preterm birth (i.e., the different preterm birth subtypes), or if it acts indirectly through its association with age-dependent confounders, factors that affect birth outcome and are a function of increasing maternal age (e.g., medical problems during pregnancy and pregnancy complications). Therefore, the aim of this study is to determine if older maternal age at first birth is an independent risk factor for spontaneous preterm labour (spontaneous labour leading to delivery at < 37 completed weeks gestation that is not associated with either ruptured membranes or iatrogenic intervention) (Ananth et al., 2005) or a risk marker that exerts its influence indirectly through other age-dependent risk factors.

The specific methodology used to address this inquiry is important. From the studies reviewed it has become apparent that it will be necessary to decide on the choice of reference group based on the age associated with optimal reproduction (less risk to pregnancy outcomes) and to control for age-dependent confounders, other risk factors and interactions among these variables.

Although there have been numerous researchers examining the etiologic factors influencing preterm birth, the majority have treated this birth outcome as a single entity. The research reviewed here indicates that preterm birth may consist of separate etiological pathways that need to be considered if this adverse birth outcome is to be fully understood. While the results of these studies are equivocal, they are also fewer in numbers. Methodological limitations in previous studies justify the need for more etiological research where the heterogeneity of preterm birth is acknowledged, and the causal mechanisms of each preterm birth subtype are examined. As delineated by Berkowitz et al. (1998), investigation into the "components" of preterm birth must continue until the "components" appear to be homogeneous. Only then can preterm birth as a "whole" be considered. Ignoring the heterogeneity of preterm birth at this point may impede our ability to determine conclusively any differential effects that older maternal age has on the varying pathways leading to early delivery.

Findings from this study will provide further insight into the relationship between older maternal age and spontaneous preterm labour. It will be the first study to have maternal age as the independent variable of interest and to be focussed on determining the direct and indirect effects of various previously identified etiologic determinants of spontaneous preterm labour (i.e., spontaneous labour leading to delivery at < 37 completed weeks gestation that is not associated with either ruptured membranes or iatrogenic intervention) (Ananth et al., 2005). As in Lang et al. (1996) pregnancy complications will be treated as intermediate outcomes of spontaneous preterm labour and entered towards the end of the risk modeling so that the mediating effects of these risk factors can be examined. Unlike previous research, the heterogeneity of the maternal population will be taken into account by comparing two risk models, one for nulliparous women who are healthy throughout their pregnancies (low risk) versus one for healthy nulliparous women who develop one or more pregnancy complications (high risk). These separate models will help to demonstrate any differences in the causal mechanisms that exist for these two groups of women.

The lack of population-based studies incorporating maternal age as the independent variable was evident from the studies reviewed. This will be the first population-based study to have older maternal age as the independent variable and one preterm birth subtype (preterm birth due to spontaneous labour) as the dependent variable. Finally, in this study there will be smaller maternal age groupings in order to more clearly establish where the "at risk" age for spontaneous preterm labour begins and to determine if there is a differential risk effect. Establishing the direct or indirect effect of older maternal age at first birth on spontaneous preterm labour in both low risk and high risk women will help to improve the quality of counseling and preterm birth prevention efforts for women of childbearing age.

Table 1

††*Characteristics and Results of the Studies Examining the Effect of Older Maternal Age on the Risk of Spontaneous Preterm Labour*

[1,2]**Aldous, M.B., Edmonson, B. (1993). Maternal age at first birth and risk of low birth weight and preterm delivery in Washington State.**			
Sample: USA; *n* = 16,492 white, first born infants delivered in Washington State between 1984 and 1988. Included *n* = 4,403 black infants. Population-based study.	**Purpose:** to study the effect of delayed childbearing on the risk of low birth weight (LBW; < 2500g), very low birth weight (< 1500g) and preterm delivery. **Design:** retrospective cohort study. **Methods:** used Washington State birth certificates. Gestational age (GA) was confirmed by first day of last menstrual period (LMP; 80% accurate; excluded cases with unknown gestational age). **Risk factors & covariates included:** hypertension, paternal and maternal occupation, marital status, smoking, prenatal care, prior fetal loss, and cesarean delivery. Pre-eclampsia, gestational diabetes and diabetes mellitus assessed but not included in final model. **Birth outcome:** PT-both (adjusted for cesarean delivery in analysis).	**Results:** AOR for PT-both = 1.0 (0.86, 1.3) for white women aged 25-29 years; 1.4 (1.1, 1.7) for white women aged 30-34 years; 1.6 (1.4, 2.0) for white women aged 35-39 years; 1.8 (1.3, 2.6) for white women aged ≥ 40 years No statistically significant findings for black women (small sample size). Reference age group: 20-24 years	**Discussion:** older maternal age a significant risk factor for PT-both in white, nulliparous women. Risk increases as a function of increasing maternal age (1.4 to 1.6 to 1.8 for women 30-34 years, 35-39 years, and ≥ 40 years, respectively, when compared with women 20-24 years of age).
Berkowitz, G.S. (1985). Clinical and obstetric risk factors for preterm delivery.			
Sample: USA; *n* = 488 infants (175 preterm, 313 term infants) delivered at Yale-New Haven Hospital between 1977 and 1978. Hospital-based study.	**Purpose:** to study the clinical and obstetric risk factors of preterm delivery. **Design:** case-control study. **Methods:** study data obtained from a structured interview and hospital delivery records. GA was confirmed by Dubowitz score. **Risk factors & covariates included:** first trimester bleeding, antepartum hemorrhage, third trimester urinary tract infection, sociodemographic factors, maternal height, pre-pregnancy weight, weight gain, previous preterm delivery, reproductive history, and incompetent cervix. **Birth outcome:** PT-both (restricted to preterm births preceded by spontaneous labour or spontaneous rupture of membranes).	**Results:** Crude OR for PT-both = 1.8 (1.2, 2.6) for women under 25 years of age (compared to those over 25 years of age) Reference age group: not reported for multivariate analysis	**Discussion:** in the multivariate analysis maternal age was not a significant predictor of preterm birth preceded by spontaneous labour or spontaneous rupture of membranes (odds ratio estimate not reported).

Table 1 (continued)

Characteristics and Results of the Studies Examining the Effect of Older Maternal Age on the Risk of Spontaneous Preterm Labour

[2]**Berkowitz, G.S., Blackmore-Prince, C., Lapinski, R.H., Savitz, D.A. (1998). Risk factors for preterm birth subtypes.**			
Sample: USA; *n* = 31,107 births at Mount Sinai Hospital between 1986 and 1994 (randomly selected one pregnancy for women who had more than one eligible pregnancy). Hospital-based study.	**Purpose:** to examine the epidemiologic risk factors for the preterm birth subtypes. **Design:** retrospective cohort study. **Methods:** used computerized perinatal database. GA confirmed by LMP and ultrasound. If menstrual date was missing, used best clinical judgement. **Risk factors & covariates included:** pre-existing medical conditions (e.g., diabetes, hypertensive disorder); pregnancy complications; sociodemographic, lifestyle, obstetric, and nutritional factors. **Birth outcome:** preterm PROM (preterm birth preceded by preterm premature rupture of membranes), preterm labour (onset of labour before rupture of membranes leading to preterm birth).	**Results:** AOR for preterm PROM = 1.4 (1.2, 1.6) for women aged 30-34 years; 1.5 (1.3, 1.8) for women aged ≥ 35 years. AOR for preterm labour = 0.95 (0.8, 1.1) for women aged 30-34 years; 0.93 (0.8, 1.1) for women aged ≥ 35 years. Reference age group: 20-29 years	**Discussion:** older maternal age (30-34 years and ≥ 35 years) significant for preterm birth due to preterm premature rupture of membranes only.
[2]**Harlow, B.L., Frigoletto, F.D., Cramer, D.W., et al. (1996). Determinants of preterm delivery in low-risk pregnancies.**			
Sample: USA; *n* = 14,948 low risk participants from the Routine Antenatal Diagnostic Imaging with Ultrasound Study (RADIUS). Excluded women with pre-existing medical conditions (i.e. diabetes mellitus, chronic hypertension, chronic renal disease).	**Purpose:** to examine potential risk factors associated with each category of preterm birth in low-risk pregnancies (i.e., no medical indication for ultrasound at first obstetrical visit). **Design:** randomized clinical trial that recruited subjects from 109 obstetrical and family practices. **Methods:** used personal interview and hospital and obstetrical office medical records. GA confirmed by LMP and ultrasound. **Risk factors & covariates included**: parity, prior LBW infant, race, abnormal glucose load, urine protein, smoking (past and present), serum alpha-fetoprotein, infant sex, positive urine culture, and pre-pregnancy weight/height. **Birth outcome:** spontaneous preterm labour (preterm birth with spontaneous labour and membranes intact), preterm PROM (preterm birth with PROM with or without spontaneous labour).	**Results:** RR (relative risk) for preterm PROM = 1.25 for women > 30 years of age (no confidence interval or p-value reported, but stated as an increased risk). Not adjusted for potential confounders. Reference age group 20-30 years of age. When adjusted for other risk factors, the RR for preterm PROM (maternal age per 5 years) = 1.3 (1.0, 1.5).	**Discussion:** stated in research discussion that maternal age predictive for preterm PROM only (p. 446). Not significant for spontaneous preterm labour.

Table 1 (continued)

Characteristics and Results of the Studies Examining the Effect of Older Maternal Age on the Risk of Spontaneous Preterm Labour

Heaman, M.I., Blanchard, J.F., Gupton, A.L., Moffatt, M.E.K., Currie, R.F. (2005). Risk factors for spontaneous preterm birth among Aboriginal and non-Aboriginal women in Manitoba.			
Sample: Canada; *n* = 684 (226 preterm and 458 term; 82 preterm Aboriginal and 176 term Aboriginal) infants delivered at two tertiary care hospitals in Winnipeg, Manitoba between October 1999 and December 2000. Hospital-based study.	**Purpose:** to identify risk factors for spontaneous preterm birth and to compare risk factors among Aboriginal and non-Aboriginal women. **Design:** case-control study. **Methods:** used labour and delivery log books, standardized questionnaire, and an in person interview. GA confirmed by LMP and ultrasound. **Risk factors & covariates included:** sociodemographic, behavioural, psychosocial, and biomedical risk factors (e.g., vaginal bleeding, gestational hypertension, urinary tract infection). **Birth outcome:** PT-both (preterm delivery preceded by spontaneous labour or rupture of the membranes without induction or elective cesarean section).	**Results:** Crude OR for PT-both = 1.27 (0.74, 2.19) for non-Aboriginal women aged >35 years. Crude OR for PT-both = 1.07 (0.31, 3.66) for Aboriginal women aged > 35 years. Older maternal age not a significant risk factor for PT-both, so not included in the final analysis. Reference age group: 19-35 years	**Discussion:** older maternal age does not increase the risk of PT-both in Aboriginal and non-Aboriginal women.
Kramer, M.S., McLean, F.H., Eason, E.L., Usher, R. (1992). Maternal nutrition and spontaneous preterm birth.			
Sample: Canada; *n* = 13,102 infants born at Montreal's Royal Victoria Hospital between 1 January 1980 and 31 March 1989 (8,022 births < 37 weeks gestation used for regression analysis; 10,358 births < 34 weeks and < 32 weeks gestation used for regression analysis). Hospital-based study.	**Purpose:** to investigate the impact of maternal nutrition and other determinants on delivery prior to 37 weeks, 34 weeks, and 32 weeks gestation. **Design:** retrospective cohort study. **Methods:** used McGill Obstetric and Neonatal Database. GA confirmed by LMP and ultrasound (dates required to agree within +/- 7 days). **Risk factors & covariates included:** pregnancy-induced hypertension, pre-pregnancy hypertension, prior at-risk obstetrical history, diabetes, urinary tract infection, height, education, marital status, smoking, and alcohol. **Birth outcome:** PT-both (includes spontaneous preterm births and preterm cesarean deliveries due to medical complications)	**Results:** AOR for women aged ≥ 35 years and delivering an infant < 37 weeks gestation = 1.13 (0.98, 1.24). AOR for women aged ≥ 35 years and delivering an infant < 34 weeks gestation = 1.15 (0.93, 1.41). AOR for women aged ≥ 35 years and delivering an infant < 32 weeks gestation = 1.05 (0.79, 1.40) Reference age group: 20-34 years	**Discussion:** older maternal age not a significant risk factor for PT-both.

Table 1 (continued)

Characteristics and Results of the Studies Examining the Effect of Older Maternal Age on the Risk of Spontaneous Preterm Labour

Lang, J.M., Lieberman, E., Cohen, A. (1996). A comparison of risk factors for preterm labor and term small-for-gestational-age birth.			
Sample: USA; n = 11,505 women recruited into the delivery interview program conducted at the Boston Hospital for Women from August 1977 to March 1980 (n = 9,490 for preterm analysis). Excluded women with menstrual abnormalities for whom gestational dating was problematic and women with pre-existing chronic diseases (i.e. diabetes mellitus, hypertension, epilepsy, asthma). Hospital-based study.	**Purpose:** to determine the effect of 23 risk factors on the prevalence of prematurity and fetal growth retardation in healthy women and to compare the different risk models. **Design:** cohort study. **Methods:** used interviews and medical records. GA confirmed by LMP. **Risk factors & covariates included:** urinary tract infection; genetic and constitutional, sociodemographic, obstetrical, nutritional, and lifestyle factors; and prenatal care. Pregnancy complications treated as intermediate outcomes (no effect on AOR for maternal age adding these factors into the risk model last). **Birth outcome:** PT-both (excluded women whose pregnancies were artificially interrupted before term).	**Results:** AOR for PT-both = 1.1 (0.8, 1.6) for women aged ≥ 35 years. Reference age group: 25-34 years	**Discussion:** older maternal age (≥ 35 years) not a significant predictor of spontaneous preterm birth.
Mercer, B.M., Goldenberg, R.L., Das, A., Moawad, A.H., et al. (1996). The preterm prediction study: A clinical risk assessment system.			
Sample: USA; n = 2,929 women participating in the Preterm Birth Prediction Study between October 1992 and July 1994 (followed up at 10 participating centres; assessed between 23 and 24 weeks gestation).	**Purpose:** to develop a risk assessment system for predicting preterm delivery preceded by spontaneous labour or preterm PROM. **Design:** prospective cohort. **Methods:** used structured interview, medical records, laboratory testing and medical exams. GA confirmed by LMP and/or ultrasound. **Risk factors & covariates included:** assessed numerous risk factors to develop a risk assessment model, including pre-existing medical conditions and pregnancy complications. **Birth outcome:** PT-both (included infants delivered before 37 weeks gestation after spontaneous labour or preterm PROM).	**Results:** Crude RR for PT-both = 1.1 (0.8, 1.6) for nulliparous women >35 years of age. Crude RR for PT-both = 1.08 (0.61, 1.92) for multiparous women > 35 years of age. Reference age group: 16-35 years.	**Discussion:** older maternal age (> 35 years) was not a significant predictor of PT-both for nulliparous or multiparous women, so it was not included in the final model.

Table 1 (continued)

Characteristics and Results of the Studies Examining the Effect of Older Maternal Age on the Risk of Spontaneous Preterm Labour

Abbreviation	Term	Description
preterm PROM	Preterm premature rupture of membranes	The rupture of chorioamniotic membranes anytime before the onset of labour prior to 37 weeks completed gestation (Newburn-Cook & Onyskiw, 2005).
RR	Relative risk	A "ratio of risk" estimated in cohort studies. For example, in the studies reviewed where PT-both is the outcome, relative risk is defined as the incidence of PT-both in women 35 years of age and older divided by the incidence of PT-both in the reference age group (e.g., women under the age of 35 years). A relative risk greater than 1.0 and a 95% confidence interval not including 1.0 indicates that there is an increased risk of PT-both for women 35 years of age and older (Newburn-Cook & Onyskiw, 2005).
OR	Odds ratio	An estimate of the relative risk in case-control studies. It is the probability or likelihood of PT-both, spontaneous preterm labour, or preterm PROM occurring for women 35 years of age and older when compared to women of younger maternal age. An odds ratio greater than 1.0 and a 95% confidence interval not including 1.0 indicates that the probability of PT-both, spontaneous preterm labour, or preterm PROM is greater for women of older maternal age (Newburn-Cook & Onyskiw, 2005).
AOR	Adjusted odds ratio	Estimates the independent effect of older maternal age on PT-both, spontaneous preterm labour, or preterm PROM after controlling for the effects of age-dependent (e.g., pre-existing medical conditions) and other potential confounders (e.g., psychosocial, behavioural, nutritional factors) (Newburn-Cook & Onyskiw, 2005).

[††] table adapted from Newburn-Cook & Onyskiw, 2005

Note. Studies adjusted for maternal age or included maternal age as the independent variable; study samples included only singleton, live births, unless separate analysis provided for multiple births and/or stillbirths; in all studies preterm birth and preterm delivery defined as delivery < 37 weeks gestation

[1] the impact of maternal age is the primary focus of the study

[2] results show significant association between older maternal age and PT-both, spontaneous preterm labour, or preterm PROM

CHAPTER 3 – METHODS

Study Design

A retrospective population-based cohort study was used to determine the impact of older maternal age at first birth on the risk of spontaneous preterm labour in Northern and Central Alberta.

Study Objectives

The specific study objectives were: 1) to determine if older maternal age at first birth was an independent risk factor for spontaneous preterm labour (defined as spontaneous labour leading to delivery at < 37 completed weeks gestation that is not associated with either ruptured membranes or iatrogenic intervention) or a risk marker that exerted its influence indirectly through other age-dependent confounders (e.g., medical problems during pregnancy such as gestational diabetes, and pregnancy complications such as pregnancy-induced hypertension); and 2) to establish separate risk models for healthy low risk nulliparous women (i.e., had no pre-existing chronic illnesses and did not develop pregnancy complications), and healthy high risk nulliparous women (i.e., had no pre-existing chronic illnesses, but developed one or more pregnancy complications). For the development of all risk models, older maternal age at first birth was classified as those women who were ≥ 35 years of age at time of delivery.

Study Subjects

The study population consisted of *N* = 193,575 women who were residents of, and gave birth in Northern and Central Alberta between January 1, 1996 and

December 31, 2004. Subjects included all Alberta women who delivered a live born, singleton infant. Cases were comprised of nulliparous women 35 years of age and older who delivered a live born, singleton infant at less than 37 completed weeks gestational age and for whom the delivery was spontaneous (not associated with either ruptured membranes or iatrogenic intervention) (Ananth et al., 2005). Controls were nulliparous women aged 25 to 29 years of age (considered the optimal age for childbearing) who delivered a live born, singleton infant between 37 and 40 completed weeks gestation, and for whom the delivery was spontaneous (not associated with either ruptured membranes or iatrogenic intervention).

The decision to define ≥ 41 completed weeks gestational age as postterm was made as a result of a committee opinion published by the Society of Obstetricians and Gynaecologists of Canada (SOGC). In this document it is stated that "the risk of adverse perinatal outcome may increase as early as 41 completed weeks" gestation (Hannah & Maternal-Fetal Medicine Committee, 1997, p. 2). Because gestational age was defined as completed weeks of gestation in the Alberta Perinatal Health Program (APHP) North Perinatal Database and because of the opinion expressed by the SOGC, ≥ 41 completed weeks gestational age was considered postterm in this study.

The study focus was restricted to singleton births because preterm birth rates and causal mechanisms differ between singleton and multiple births (Demissie et al., 2001; Joseph et al., 1998). Medically indicated preterm births, defined as births that follow iatrogenic intervention (i.e., labour induction or a primary or repeat cesarean delivery) (Ananth et al., 2005), and births occurring as a result of ruptured membranes were excluded for both cases and controls.

Data Source

Maternal and newborn data recorded in the APHP North Perinatal Database were used for this study. This is one of two regional perinatal databases maintained by the APHP. Data are collected from health care facilities that provide maternal and newborn care in Health Regions 4 through 9. This computerized population-based perinatal database contains pregnancy and birth data recorded on the provincial delivery records (Parts 1 and 2) by hospital staff prior to and at the time of delivery. These provincial delivery records are completed for all deliveries. The database also includes information on home births attended by registered midwives. The only deliveries not captured in the APHP database are those births women choose to conceal or deliveries overseen by an unregulated birth attendant.

Perinatal data are recorded based on the place of delivery and this information is forwarded to the APHP for data entry. Data collected by participating hospitals are forwarded to the APHP using one of three methods: 1) photocopies of the provincial delivery records; 2) a log book that is transcribed from the provincial delivery records; or, 3) electronic transfer of the data from the provincial delivery records.

A number of precautions are taken to ensure both completeness and accuracy of the data entered into the APHP databases. After the data are entered, a data validation procedure is implemented. This consists of a monthly crosscheck of the manual tabulation of key variables with an electronic tabulation of these same variables. A minimum of 1 in 20 records is verified with the actual data entry to check its accuracy. Participating hospitals are provided with guidelines for validating electronic data so that validation of hospital data can occur before it is sent to the APHP. In addition, the APHP completes a validation process for electronically submitted data. This consists of electronic tabulation and comparison of results with the Monthly Statistical Report that is supplied with the data.

The APHP North Perinatal Database includes information on genetic and constitutional factors, maternal age at time of delivery, lifestyle factors, obstetrical history, medical problems in the current pregnancy, pregnancy complications, birth outcomes and limited information about the infant. This database also contains information on maternal health status including the presence of any pre-existing chronic diseases.

Study Variables

The outcome (dependent variable) in this study was spontaneous preterm labour. It was defined as spontaneous labour leading to the delivery of a live born, singleton infant prior to 37 completed weeks gestational age that was not associated with either ruptured membranes or iatrogenic intervention (i.e., labour induction or a primary or repeat cesarean delivery) (Ananth et al., 2005). Of particular interest in the study was the impact of older maternal age (independent variable) on the risk of spontaneous preterm labour. Older maternal age was defined as women who delivered their first child at 35 years of age or older.

There is some controversy in the literature regarding what constitutes older maternal age. Are women aged 35 to 39 years at an increased risk for preterm birth if they are in good health? Does the risk increase among older nulliparous women regardless of health status during pregnancy? Or does the risk for adverse birth outcomes start earlier, as some researchers suggest, for women at the age of 30 years as opposed to later (Aldous & Edmonson, 1993; Berkowitz et al., 1998)? Therefore, to assess the impact of maternal age on the risk of spontaneous preterm labour, maternal age was stratified into the following age categories: 20 to 24 years, 25 to 29 years (reference group), 30 to 34 years, and ≥ 35 years. By stratifying maternal age in this manner, there was a clearer indication of where the older "at risk" maternal age began for spontaneous preterm labour, and the occurrence of any differential age effects was established in the risk modeling.

Other risk factors and age-dependent covariates (independent variables) were included in the risk models to examine the impact of older maternal age on the risk of spontaneous preterm labour for low risk and high risk women. These factors are outlined in Table 2 and include maternal and newborn factors, obstetric and medical factors, lifestyle behaviours, medical problems arising during pregnancy, and pregnancy complications. The variables selected for inclusion in this study were based on two reviews of the published literature that focused on the etiology of preterm birth. In particular, the systematic review and meta-analysis completed by Kramer (1987), and the review of the epidemiology of preterm birth (risk factors causally related to decreased gestational age) by Berkowitz and Papiernik (1993), guided the selection of other independent variables to be included in the risk models (see Table 2).

The risk modeling was limited to maternal and clinical variables recorded in the APHP North Perinatal Database, and the way in which these potential risk factors were measured or aggregated. Consequently, only a partial risk model could be provided. A full explanatory model would require further research, and consideration of other potential determinants not recorded in the data source (perinatal database) used in this study. This is a limitation of using administrative data in the conduct of etiological research.

Table 2

Risk Factors Included in the Study

Demographic

- Maternal age (≥ 20 years stratified into 4 age categories: 20 to 24 years, 25 to 29 years, 30 to 34 years, and ≥ 35 years)

Genetic and Constitutional

- Maternal height (< 152 cm or ≥ 152 cm)
- Pre-pregnancy weight (≤ 45 kg, 46-90 kg, ≥ 91kg)

Lifestyle factors

- Smoker (smoked anytime during pregnancy)
- Alcohol consumption (defined as any alcohol consumed during pregnancy, ≥ 1 drink/day throughout pregnancy, or ≥ 3 drinks on any one occasion during pregnancy)
- Drug dependent (inappropriate/excessive use of any substance which may adversely affect pregnancy outcome)

Nutritional problems during pregnancy

- Poor gestational weight gain (< 0.5 kg/wk. or weight loss between 26 to 36 completed weeks gestation)
- Anemia (hemoglobin < 100g/l)

Table 2 (continued)

Risk Factors Included in the Study

Medical problems during current pregnancy (for Model 2 only – Figure 2)

- Gestational diabetes
- Poly/oligohydramnios
- Presence of blood antibodies (RH, Anti-C, Anti-K, etc.)
- Acute medical disorder (e.g. urinary tract infection, acute asthma, thyrotoxicosis)

Current pregnancy status (for Model 2 only – Figure 2)

- Diagnosis of a small-for-gestational age (SGA) infant (< 10th percentile)
- Diagnosis of a large for gestational age (LGA) infant (> 90th percentile)
- Presence of a fetal anomaly
- Fetal malpresentation

Pregnancy complications (for Model 2 only – Figure 2)

- Placenta previa
- Bleeding < 20 completed weeks gestation, bleeding ≥ 20 completed weeks gestation, or bleeding throughout pregnancy
- Pregnancy-induced hypertension (PIH)
- Pre-eclampsia/eclampsia (defined as the presence of PIH with proteinuria (≥ +1) and/or the presence of seizures)

Data Analysis

The APHP data were cleaned and analyzed using SPSS for Windows Version 14.0 (SPSS Inc., Chicago, IL). Each study variable was examined for outliers (implausible values) and coding errors which were corrected if feasible, or coded as missing values. New variables were created as required from existing variables in the database using the "transform re-code" command in the SPSS data analysis program.

The prevalence and distribution of the study variables were summarized by group (i.e., all births preceded by spontaneous labour and cases vs. controls) in Chapter 4 using descriptive statistics. Means and standard deviations (*SD*) were calculated for continuous variables, while frequencies and percentages were used to summarize categorical variables. To determine if the prevalence and distribution of variables across the study groups were different, a chi-square test for proportions was calculated. A two-sided p-value < 0.05 was used to establish if any of the compared differences between cases and controls were statistically significant.

Univariate logistic regression was used to determine the contribution of every predictor (independent) variable on the incidence of spontaneous preterm labour, without controlling for the influence of other risk factors and potential covariates. Unadjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated and reported in Chapter 4 to indicate the magnitude and direction of the effect of each independent variable on the likelihood of delivering a preterm baby following spontaneous labour. A significant OR (greater than 1.0) indicated that women exposed to the risk factor had a higher risk of delivering a preterm infant following spontaneous labour than women who were not exposed to the risk factor. All significant risk factors and covariates from the univariate analysis were included in the subsequent multivariate logistic regression (MLR) analysis.

Unconditional MLR was conducted and carried out in three stages. First, the independent effect of each study variable (risk factor) on the risk of spontaneous preterm labour was assessed, while simultaneously controlling for all the other study variables and covariates in the absence of interaction effects (Hosmer & Lemeshow, 2000). Second, a test for confounding was done for insignificant risk factors from Stage 1. The presence of confounding was established by calculating the difference between the unstandardized beta coefficients for significant risk factors remaining in the model. If the difference (absolute value) between the unstandardized beta coefficient with the confounder in the model and the unstandardized beta coefficient without the confounder in the model was greater than 15%, then confounding was indicated and the confounder was added back into the risk model (Hosmer & Lemeshow, 2000).

The third stage in the multivariate analysis consisted of testing for interaction effects among significant predictors from Stage 1 and confounders from Stage 2. The significance of each possible interaction was assessed individually by entering each interaction term one at a time to assess for significance. Only those interactions contributing significantly to the regression model were left in the final model.

The final regression model incorporated all significant predictors of spontaneous preterm labour, as well as any confounders and significant interactions

(Hosmer & Lemeshow, 2000). The amount of variance explained by the final regression model was calculated by dividing the final model chi-square by the original –2 log likelihood (before any variables were entered) (Field, 2000). Adjusted odds ratios (AOR) and 95% CIs for the MLR are reported in Chapter 4 (see Tables 3 to 6).

Tests for confounding and the selection of the interaction terms were based on the results of previous studies. For example, researchers have found that the incidence of gestational diabetes and pregnancy complications increases as maternal age increases (Jacobsson, Ladfors, & Milsom, 2004; Jolly et al., 2000; Joseph et al., 2005; Salihu, et al., 2003). Furthermore, it has been demonstrated that the effect of smoking on preterm birth is greater as maternal age advances (Cnattinguis, Forman, Berendes, Graubard, & Isotalo, 1993; Wen et al., 1990) and that a person who smokes is more likely to use illicit drugs and alcohol (Visscher, Feder, Burns, Brady, & Bray, 2003). These possible relationships among risk factors provided direction as to what confounding and interaction effects were assessed in the present study.

Separate risk models were developed to examine the impact of older maternal age on the risk of spontaneous preterm labour for healthy low risk nulliparous women (had no pre-existing chronic illnesses and did not develop pregnancy complications) and healthy high risk nulliparous women (had no pre-existing chronic illnesses, but developed one or more pregnancy complications). The study variables were entered in a stepwise fashion in blocks as outlined in Figures 1 and 2. This was done to determine if older maternal age had an independent (direct) or an indirect effect (mediated through other factors including age-dependent variables) on the dependent variable (i.e., spontaneous preterm labour). The hypothetical models (see Figures 1 and 2) were based on the risk model used by White (2004) to determine the direct and indirect effects of previously identified risk factors on birth weight and gestational age.

A number of factors guided the development of these models and the order in which the individual study variables and interaction effects were entered. These included: 1) consideration of the risk factors that were present prior to the current pregnancy (e.g., maternal age, height, pre-pregnancy maternal weight); 2) reflection on the proximal and distal causes and the pathways leading to preterm birth; 3) examination of the relationships between the different study variables (e.g., maternal age may influence the development of pregnancy complications which necessitate preterm delivery); and 4) consideration of the interaction among different variables and their differential impact on the risk of preterm birth (White, 2004).

The risk factors outlined in Figures 1 and 2, and their order of entry into the logistic regression models reflects the distal and proximal relationship of each risk factor to the dependent variable. For example, maternal age was considered the most distal risk factor in the proposed models because it was assumed that subsequent risk factors were a function of maternal age (e.g., problems in the index pregnancy, the development of one or more pregnancy complications). These figures do not distinguish between indirect and direct effects of the risk factors on spontaneous preterm labour.

Pregnancy complications were assumed to be intermediate (intervening) pregnancy outcomes, and hence were entered last into the regression analysis before the interaction terms. If pregnancy complications were entered earlier into the risk models, this could have led to an underestimation or elimination of the effect of maternal age on spontaneous preterm labour whose impact may be mediated through pregnancy complications (Lang et al., 1996; Kramer, 1987). Each pregnancy complication was entered separately to assess both the direct or indirect effect of each complication on spontaneous preterm labour. Interactions were entered last into the risk model one at a time, in order to assess which interactions remained significant in the MLR (see Figures 1 and 2). Only interactions for risk factors remaining in the model after the univariate analysis, and Stage 1 and Stage 2 of the MLR were assessed.

In the past, researchers have arbitrarily chosen the reference group for maternal age comparisons in MLR analyses. Because maternal age was stratified into four different groups in this study (i.e., 20 to 24 years, 25 to 29 years, 30 to 34 years, and ≥ 35 years), the choice of reference group for maternal age was determined by comparing the prevalence of preterm birth arising from spontaneous labour by maternal age. Previous research has indicated that the risk of spontaneous preterm labour could begin at 30 to 34 years of age (Aldous & Edmonson, 1993; Berkowitz et al., 1998), so only women aged 20 to 24 years and 25 to 29 years were considered as possible reference groups. A chi-square test indicated that there was a significantly lower ($p < 0.05$) prevalence of spontaneous preterm labour among healthy nulliparous women aged 25 to 29 years (3.4%) than healthy nulliparous women aged 20 to 24 years (4.1%). Therefore, healthy nulliparous women aged 25 to 29 years were used as the reference group for maternal age in all MLR analyses.

Figure 1

Model 1 (Low Risk Nulliparous Women): Order of Entry of Variables into the Logistic Regression Model

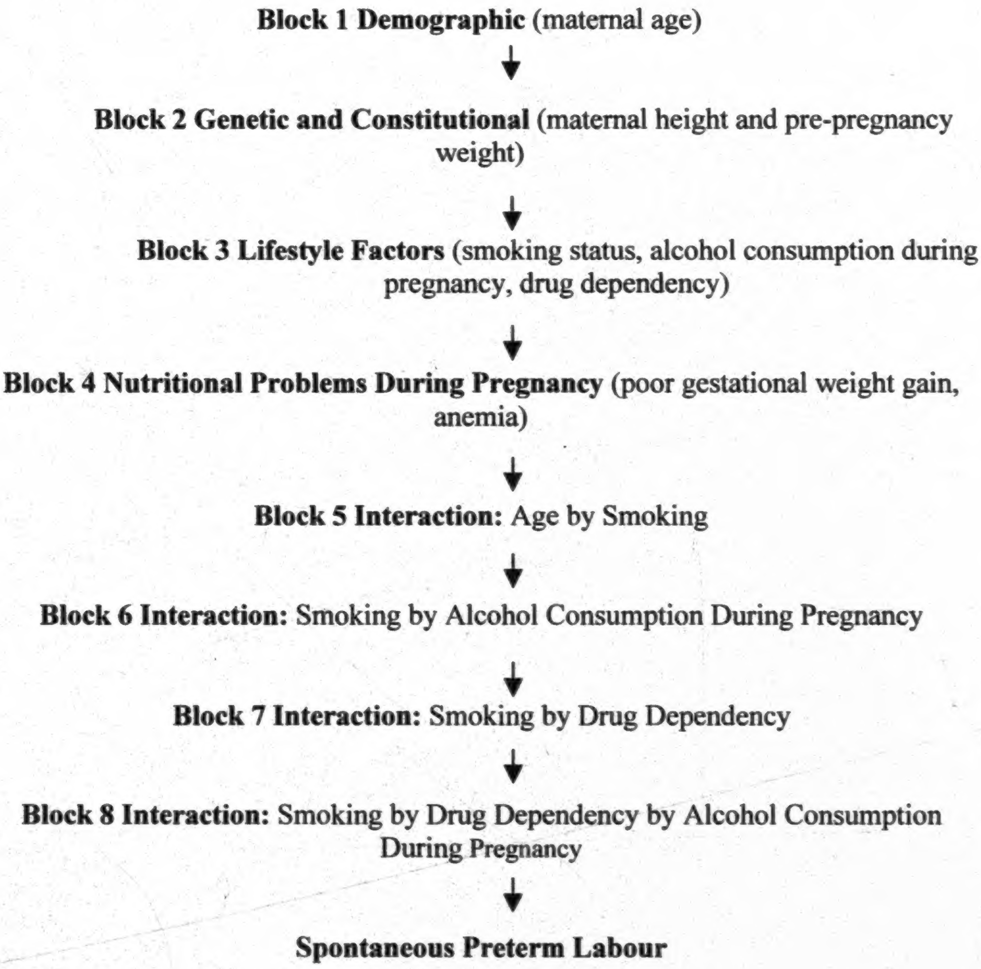
Block 1 Demographic (maternal age)
Block 2 Genetic and Constitutional (maternal height and pre-pregnancy weight)
Block 3 Lifestyle Factors (smoking status, alcohol consumption during pregnancy, drug dependency)
Block 4 Nutritional Problems During Pregnancy (poor gestational weight gain, anemia)
Block 5 Interaction: Age by Smoking
Block 6 Interaction: Smoking by Alcohol Consumption During Pregnancy
Block 7 Interaction: Smoking by Drug Dependency
Block 8 Interaction: Smoking by Drug Dependency by Alcohol Consumption During Pregnancy
Spontaneous Preterm Labour

Figure 2

Model 2 (High Risk Nulliparous Women): Order of Entry of Variables into the Logistic Regression Model

Block 1 Demographic (maternal age)

↓

Block 2 Genetic and Constitutional (maternal height and pre-pregnancy weight)

↓

Block 3 Lifestyle Factors (smoking status, alcohol consumption during pregnancy, drug dependency)

↓

Block 4 Nutritional Problems During Pregnancy (poor gestational weight gain, anemia)

↓

Block 5 Medical Problems During Current Pregnancy (gestational diabetes, poly/oligohydraminos, presence of blood antibodies, acute medical disorder)

↓

Block 6 Current Pregnancy Status (diagnosis of a SGA infant, diagnosis of a LGA infant, presence of a fetal anomaly, fetal malpresentation)

↓

Block 7 Pregnancy Complication (placenta previa)

↓

Block 8 Pregnancy Complication (bleeding < 20 weeks, bleeding ≥ 20 weeks, bleeding throughout pregnancy)

↓

Block 9 Pregnancy Complication (pregnancy-induced hypertension, i.e., PIH)

↓

Block 10 Pregnancy Complication (pre-eclampsia or eclampsia – PIH + proteinuria ≥ +1 + seizures)

↓

Figure 2 (continued)

Model 2 (High Risk Nulliparous Women): Order of Entry of Variables into the Logistic Regression Model

Block 11 Interaction: Age by Smoking

↓

Block 12 Interaction: Smoking by Alcohol Consumption During Pregnancy

↓

Block 13 Interaction: Smoking by Drug Dependency

↓

Block 14 Interaction: Smoking by Drug Dependency by Alcohol Consumption During Pregnancy

↓

Block 15 Interaction: Age by Gestational Diabetes

↓

Block 16 Interaction: Age by Fetal Anomaly

↓

Block 17 Interaction: Age by Placenta Previa

↓

Block 18 Interaction: Age by PIH

↓

Block 19 Interaction: Age by Pre-eclampsia/eclampsia

↓

Spontaneous Preterm Labour

Ethical Considerations

A research proposal was submitted to the University of Alberta Health Research Ethics Board (Panel B) for expedited review and approval. The Alberta Perinatal Health Program (APHP) as part of its audit program already collected the data required for this study. A data request was submitted to the APHP for data access and for use of the APHP database. Approval by the Alberta Health Research Ethics Board and the APHP for this study was received.

The data file provided for this study did not contain any personal identifiers, only anonymous subject ID numbers, in order to maintain subject confidentiality. Data were stored on an external hard drive, which was securely locked up when not in use. Only members of the thesis supervisory committee had access to the data in order to assist with data management and analysis. All data will be kept in a locked filing cabinet for at least seven years.

CHAPTER 4 – RESULTS

The purpose of this study was to determine the impact of older maternal age on the risk of spontaneous preterm labour (defined as spontaneous labour leading to delivery at < 37 completed weeks gestation that is not associated with either ruptured membranes or iatrogenic intervention) (Ananth et al., 2005). The specific objective was to determine if older maternal age at first birth was an independent risk factor for spontaneous preterm labour or a risk marker exerting its influence indirectly through other age-dependent risk factors.

A retrospective population-based cohort study was conducted using maternal and newborn data contained in the Alberta Perinatal Health Program (APHP) North Perinatal Database. The risk factors included in the risk modeling (see Table 2) were chosen based on two previous literature reviews (Berkowitz and Papiernik, 1993; Kramer, 1987) where the focus was the etiology of preterm birth. Because the risk modeling in this study was limited to the variables recorded in the APHP database, and the way in which they were measured or aggregated, only a partial risk model could be established.

In this chapter, the study results will be presented in the following order. First, the characteristics of the overall study population will be described (i.e., all births following spontaneous labour). Next, the prevalence of potential risk factors for all births arising from spontaneous labour will be reported; then the prevalence of selected risk factors compared across the study groups (preterm versus term births following spontaneous labour) will be summarized. Finally, the results from both the univariate and multivariate logistic regression (MLR) analyses will be detailed. The results will first be presented for low risk nulliparous women (i.e., had no pre-existing chronic illnesses and did not develop pregnancy complications) and then high risk nulliparous women (i.e., had no pre-existing chronic illnesses, but developed one or more pregnancy complications). A summary of all the results can be found in Tables 3 to 6 at the end of this chapter.

Study Population

The study population consisted of *N* = 193,575 women who were residents in Northern and Central Alberta and gave birth to a live born, singleton infant between January 1, 1996 and December 31, 2004. For this study, only nulliparous women were included in the analyses. A case-control comparison was made between preterm births (cases) and term births (controls) occurring as a result of spontaneous labour. Multiple births, multiparous women, women under 20 years of age, women with unknown age, non-Alberta residents who delivered in Alberta, and stillbirths (*n* = 133,182) were all excluded from the study cohort. In addition, term births (*n* = 14,018) and preterm births (*n* = 3,284) occurring as a result of ruptured membranes or iatrogenic intervention, infants delivered at ≥ 41 completed weeks gestation (*n* = 10,706), and births with missing data for gestational age (*n* = 294) were not included in the study cohort.

The final study sample consisted of *n* = 32,091 nulliparous women who delivered spontaneously. Of these women, *n* = 18,340 were considered low risk, while *n* = 30,208 were considered high risk. A total of *n* = 1,916 women with pre-existing diabetes, heart disease, medical disorders, hypertension and chronic renal disease, along with *n* = 23 women with missing values for these variables, were excluded from the data analysis.

The percentage of low risk women 40 years of age and older and high risk women 40 years of age and older was 0.7% and 0.8%, respectively. Because of the small numbers in each of these age categories, older maternal age was classified as ≥ 35 years for all statistical analyses, as opposed to 35 to 39 years and 40 to 49 years.

Maternal Characteristics of Low Risk Nulliparous Women

Table 3 (Column 1) summarizes the maternal characteristics for all low risk nulliparous women who delivered either a preterm or term infant following spontaneous labour in Northern and Central Alberta (*n* = 18,340). Maternal age ranged from 20 to 49 years with a mean age of 26.72 years (*SD* ± 4.63 years).

Approximately 94% (*n* = 17,216) of the women delivered their infants between 20 and 34 years of age and 6% (*n* = 1,124) delivered their infants at 35 years of age and older. The majority of women (94.2%) weighed between 46 and 90kg before pregnancy; for the remainder, 5.3% (*n* = 963) weighed ≥ 91kg and 0.6% (*n* = 102) weighed ≤ 45kg. Only 0.8% (*n* = 152) of women had poor gestational weight gain (defined as < 0.5 kg/wk. or weight loss between 26 to 36 completed weeks gestation) and 0.3% (*n* = 61) developed anemia during their pregnancy. Nineteen percent (*n* = 3,527), 2% (*n* = 338), and 0.8% (*n* = 154) of women reported that they smoked, consumed alcohol, or were drug dependent, respectively, during their pregnancy.

Prevalence of Maternal Characteristics for Low Risk Nulliparous Women who had a Preterm or Term Birth Following Spontaneous Labour

The potential risk factors for low risk nulliparous women were categorized into the following groups: demographic, genetic and constitutional, lifestyle factors, and nutritional problems. The prevalence of these potential risk factors was reported for preterm (cases) and term (controls) births arising from spontaneous labour. These results are summarized in Table 3.

The prevalence of preterm births arising from spontaneous labour among healthy low risk nulliparous women was 2.4 % (*n* = 431). The mean maternal age for women who delivered a preterm baby was slightly higher than for women who delivered a term baby (27.08 ± 4.86 years versus 26.71 ± 4.62 years) following spontaneous labour.

A chi-square analysis was conducted to determine if there was a significant difference in the prevalence of risk factors by the type of delivery (i.e., term or preterm delivery preceded by spontaneous labour). The only variables significantly related ($p < 0.05$) to type of delivery were maternal age, smoking and drug dependency. A significantly higher proportion of women aged 35 years and older delivered a preterm infant following spontaneous labour as opposed to a term infant (8.8% versus 6.1%). Moreover, a significantly higher proportion of healthy nulliparous women who delivered a preterm infant following spontaneous labour smoked (23.7% versus 19.1%) and were drug dependent during pregnancy (2.6% versus 0.8%).

Logistic Regression Analysis for Low Risk Nulliparous Women

The results from the univariate analysis for low risk nulliparous women indicated that the odds of having a preterm delivery following spontaneous labour increased for women aged 35 years and older (OR = 1.71, 95% CI = 1.19-2.46), women who smoked (OR = 1.31, 95%CI = 1.05-1.64), and women who were drug dependent (OR = 3.25, 95% CI = 1.75-6.05) (see Table 4).

Figure 1 (page 54) represents the order of risk factors for entry into the MLR analysis for low risk nulliparous women. After adjusting for the effects of smoking and drug dependency, it was found that low risk nulliparous women ≥ 35 years of age had a higher risk of spontaneous preterm labour (adjusted odds ratio or AOR = 1.71, 95% CI = 1.19-2.46). Moreover, low risk nulliparous women who were drug dependent were almost 3 times more likely to deliver a preterm infant following spontaneous labour (AOR = 2.83, 95% CI = 1.50-5.37).

Testing for the confounding effect of smoking with maternal age and drug dependency showed that smoking was a confounder with maternal age 20 to 24 years. As a result, smoking was added back into the regression model. There were no significant interaction effects for age by smoking or smoking by drug dependency. Therefore, the final regression model for low risk nulliparous women included older maternal age (≥ 35 years), drug dependency, and smoking status. This model explained 0.5% of the variance for spontaneous preterm labour.

Only maternal age ≥ 35 years and drug dependency had a direct and independent significant effect on the risk of spontaneous preterm labour among low risk nulliparous women. These findings show that older maternal age increased the risk of spontaneous preterm labour even if nulliparous women developed no pregnancy complications. However, much of the variance for spontaneous preterm labour in this group of women remains unexplained. The high percentage of variance unaccounted for in this model is most likely a result of the partial risk model used for spontaneous preterm labour in this study.

Maternal Characteristics and Reproductive Factors for High Risk Nulliparous Women

Table 5 (Column 1) summarizes the maternal characteristics and reproductive factors/outcomes for all high risk nulliparous women who delivered either a preterm or term infant following spontaneous labour in Northern and Central Alberta (*n* = 30,208). Of these women, 2.8% (*n* = 839) had at least one medical problem, 7.2% (*n* = 2,168) were diagnosed with at least one infant concern (e.g., diagnosis of small-for-gestational age), and 10.5% (*n* = 3,166) developed at least one pregnancy complication at some point during their pregnancy.

The mean maternal age for this group of women was 26.94 years (*SD* ± 4.71 years). Ninety-three percent (*n* = 28,089) delivered their first baby between 20 and 34 years of age, while 7% (*n* = 2,119) delivered their first baby at 35 years of age and older. Six percent (*n* = 1,805) weighed ≥ 91kg and 0.5% (*n* = 141) weighed ≤ 45kg; 1% (*n* = 304) had poor gestational weight gain; 0.4% (*n* = 110) had anemia during pregnancy; and 6.8% (*n* = 2,054) experienced bleeding at some point during pregnancy. Bleeding during pregnancy was the most prevalent pregnancy complication reported in this study population.

Approximately 2% (*n* = 543) and 1% (*n* = 236) of high-risk women consumed alcohol and were drug dependent, respectively, during pregnancy. Also, 19.5% (*n* = 5,888) of women reported that they smoked.

Prevalence of Maternal Characteristics and Reproductive Factors for High Risk Nulliparous Women who had a Preterm or Term Birth Following Spontaneous Labour

The prevalence of the potential risk factors for high risk nulliparous women is summarized for cases (preterm births arising from spontaneous labour) and controls (term births arising from spontaneous labour) in Table 5. The prevalence of preterm delivery following spontaneous labour was 3.9% (*n* = 1,170). The mean maternal age for high risk women delivering a preterm infant was 27.26 years (*SD* ± 5.01 years). For high risk women delivering at term, the mean maternal age was 26.92 years (*SD* ± 4.70 years).

A chi-square analysis was conducted to determine if there was a relationship between the potential risk factors for high risk women and the type of delivery (i.e., term or preterm delivery preceded by spontaneous labour). With the exception of genetic and constitutional factors (i.e., maternal height and pre-pregnancy weight), alcohol use, nutritional problems, presence of blood antibodies, and diagnosis of a large for gestational age infant, all potential risk factors were significantly related ($p < 0.05$) to type of delivery. More women ($p < 0.05$) aged 35 years and older delivered a preterm infant (9.2%) as opposed to a term infant (6.9%) following spontaneous labour and a significantly higher proportion of women who delivered a preterm infant following spontaneous labour smoked (23.2 % versus 19.3%), and were drug dependent (1.8% versus 0.7%) during pregnancy.

High risk nulliparous women who developed at least one pregnancy complication delivered a greater percentage of preterm infants than term infants ($p < 0.05$) following spontaneous labour. For example, among those women who developed pregnancy-induced hypertension (PIH), 5.8% ($n = 68$) had a preterm delivery and 2.8% ($n = 813$) had a term delivery following spontaneous labour. Among those women who developed bleeding at ≥ 20 completed weeks gestation, 12.4% ($n = 145$) had a preterm delivery and 1.8% ($n = 537$) had a term delivery following spontaneous labour.

Logistic Regression Analysis for High Risk Nulliparous Women

Table 6 outlines the results from the univariate analysis for the high risk nulliparous women. In the univariate analysis, spontaneous preterm labour occurred more frequently among women who were ≥ 35 years of age (OR = 1.56, 95% CI = 1.26-1.95), women who smoked (OR = 1.26, 95% CI = 1.09-1.44), and women who were drug dependent (OR = 2.45, 95% CI = 1.56-3.85). High risk women were at an increased risk of spontaneous preterm labour if they developed gestational diabetes (OR = 1.49, 95% CI = 1.03-2.15); experienced poly- or oligohyrdramnios (OR = 4.40, 95% CI = 2.91-6.65); had at least one acute medical disorder during their pregnancy (OR = 2.53, 95% CI = 1.16-5.51); were diagnosed with a small-for-gestational age (SGA) infant (OR = 2.50, 95% CI = 1.84-3.39), or an infant with a fetal anomaly (OR = 2.14, 95% CI = 1.39-3.28); and had a fetal malpresentation (OR = 5.46, 95% CI = 4.53-6.59). The odds of having spontaneous preterm labour also increased for women who developed pregnancy complications. The risk was greatest for women who had placenta previa (OR = 64.60, 95% CI = 27.79-150.19).

Table 6 also details the results from the MLR analysis for high risk women. Figure 2 (page 55) outlines the order of entry for the risk factors into the MLR. After controlling for all the significant risk factors from the univariate analysis (Stage 1 of the MLR), it was found that smoking (AOR = 1.15, 95% CI = 0.95-1.39), presence of an acute medical disorder (AOR = 1.06, 95% CI = 0.25-4.48), presence of a fetal anomaly (AOR = 1.71, 95% CI = 0.97-3.01), and presence of pre-eclampsia/eclampsia (AOR = 1.77, 95% CI = 0.90-3.51) were not significant predictors of spontaneous preterm labour (see Table 6, Column 2). Therefore, tests for confounding were conducted (Stage 2 of the MLR) for smoking (with maternal age and drug dependency), fetal anomaly (with older maternal age), and pre-eclampsia/eclampsia (with PIH).

Although tests for the confounding effects of smoking and fetal anomaly were chosen based on relationships established in previous research, the confounding effect for pre-eclampsia/eclampsia (i.e., PIH with proteinuria (≥ + 1) and/or seizures) was based on the relationship between pre-eclampsia, eclampsia, and PIH. Confounding effects for acute medical disorders were not tested because disorders in this category were not mutually exclusive; as this category included several disorders (e.g., urinary tract infection, acute asthma, thyrotoxicosis) so it would have been impossible to determine which medical disorder was the confounder. The only confounding effect found was between pre-eclampsia/eclampsia and PIH, so pre-eclampsia/eclampsia was added back into the MLR model.

In the third stage of the MLR, the interactions for age by gestational diabetes, age by placenta previa, age by PIH, and age by pre-eclampsia/eclampsia were entered individually to test for significance. The change in –2 log likelihood showed that the addition of age by gestational diabetes into the model was borderline significant ($p < 0.05$), while the addition of all other interactions was non-significant. Although the addition of age by gestational diabetes was borderline significant, adding this interaction term into the model did not improve the percent of variation explained. As a result, no interaction terms were included in the final model.

The final regression model for high risk nulliparous women incorporated all the significant predictors of spontaneous preterm labour, as well as pre-eclampsia/eclampsia. This model explained 7.3% of the variance for spontaneous preterm labour. The findings from the final regression model are detailed in Table 6 (Column 3).

After controlling for all the significant predictors of spontaneous preterm labour and pre-eclampsia/eclampsia, high risk nulliparous women aged 30 to 34 years (AOR = 1.25, 95% CI = 1.01-1.56) and high risk nulliparous women aged 35 years and older (AOR = 1.49, 95% CI = 1.12-1.99) had a significantly higher risk of spontaneous preterm labour than did high risk nulliparous women aged 25 to 29 years. When placenta previa was entered into the model, the AOR for women ≥ 35 years of age decreased from 1.57 (95% CI = 1.19-2.08) in the previous block to 1.50 (95% CI = 1.13-1.99), indicating that part of the older maternal age effect may have acted indirectly through placenta previa. However, even after the addition of all the pregnancy complications into the MLR, older maternal age (≥ 35 years) had a significant direct and independent effect on spontaneous preterm labour.

Other predictors with a direct and independent effect on spontaneous preterm labour included drug dependency (AOR = 2.62, 95% CI = 1.52-4.52), gestational diabetes (AOR = 2.04, 95% CI = 1.34-3.12), poly- or oligohyrdramnios (AOR = 3.23, 95% CI = 1.84-5.65), and diagnosis of a SGA infant (AOR = 2.02, 95% CI = 1.33-3.05). Although fetal malpresentation proved to have a significant effect on spontaneous preterm labour (AOR = 5.32, 95% CI = 4.15-6.82), this result was most likely a reflection of an effect rather than a cause. For instance, once labour started, the baby became malpositioned in the birth canal as a result of its small size.

The vast majority of pregnancy complications were significant predictors of spontaneous preterm labour. Placenta previa (AOR = 22.56, 95% CI = 8.73-58.30), bleeding at < 20 completed weeks gestational age (AOR = 1.49, 95% CI = 1.07-2.08), bleeding at ≥ 20 completed weeks gestational age (AOR = 5.86, 95% CI = 4.44-7.73), bleeding throughout pregnancy (AOR = 7.09, 95% CI = 4.34-11.57), and PIH (AOR = 1.80, 95% CI = 1.20-2.70) all had a direct and independent impact on spontaneous preterm labour.

Summary of Major Findings

Older maternal age had a significant independent and direct effect on spontaneous preterm labour for healthy nulliparous women who did not develop pregnancy complications (low risk). Overall, low risk nulliparous women 35 years of age and older were over 1.5 times more likely to develop spontaneous preterm labour than low risk nulliparous women aged 25 to 29 years. Furthermore, low risk nulliparous women who were drug dependent were at the greatest risk of spontaneous preterm labour (AOR = 2.83, 95% CI = 1.50-5.37).

For healthy nulliparous women who developed one or more pregnancy complications (high risk), maternal age had a direct and independent effect on spontaneous preterm labour. Increased risk for spontaneous preterm labour in this group of women began at age 30 to 34 years (AOR = 1.25, 95% CI = 1.01-1.56). Older high risk nulliparous women (≥ 35 years of age) were 1.5 times more likely to develop spontaneous preterm labour. Although part of the older maternal age effect may have acted indirectly through placenta previa, older maternal age still had a significant independent and direct effect on spontaneous preterm labour, even after the addition of all pregnancy complications into the model.

Other significant predictors of spontaneous preterm labour for high risk nulliparous women included drug dependency, gestational diabetes, poly/oligohydramnios, diagnosis of a SGA infant, placenta previa, bleeding during pregnancy, and PIH. The AORs for these risk factors ranged from 1.49 (bleeding < 20 completed weeks gestational age) to 22.56 (placenta previa). High risk nulliparous women with placenta previa were at the greatest risk of having a preterm birth preceded by spontaneous labour. Although fetal malpresentation was significantly related to spontaneous preterm labour, it was seen as an effect of having early labour and a SGA baby rather than a “cause” of spontaneous preterm labour.

Table 3

Maternal Characteristics for Preterm and Term Births Following Spontaneous Labour in Low Risk Nulliparous Women

CHARACTERISTICS	ALL SPONTANEOUS LABOUR *n* = 18,340 *n* (%)	TERM SPONTANEOUS LABOUR *n* = 17,909 *n* (%)	PRETERM SPONTANEOUS LABOUR *n* = 431 *n* (%)
Maternal age (years) (mean ± *SD*)	**26.72 ± 4.63**	**26.71 ± 4.62**	**27.08 ± 4.86**
Demographic			
*Maternal age (years)			
20-24	6,635 (36.2)	6,474 (36.1)	161 (37.4)
25-29	6,782 (37.0)	6,646 (37.1)	136 (31.6)
30-34	3,799 (20.7)	3,703 (20.7)	96 (22.3)
≥ 35	1,124 (6.1)	1,086 (6.1)	38 (8.8)
Genetic and Constitutional			
Maternal height (cm)			
≥ 152	17,997 (98.1)	17,576 (98.1)	421 (97.7)
< 152	343 (1.9)	333 (1.9)	10 (2.3)
Maternal pre-pregnancy weight (kg)			
≤ 45	102 (0.6)	97 (0.5)	5 (1.2)
46-90	17,275 (94.2)	16,869 (94.2)	406 (94.2)
≥ 91	963 (5.3)	943 (5.3)	20 (4.6)
Lifestyle Factors			
*Smoking			
No	14,813 (80.8)	14,484 (80.9)	329 (76.3)
Yes	3,527 (19.2)	3,425 (19.1)	102 (23.7)
Alcohol use			
No	18,002 (98.2)	17,579 (98.2)	423 (98.1)
Yes	338 (1.8)	330 (1.8)	8 (1.9)
*Drug dependency			
No	18,186 (99.2)	17,766 (99.2)	420 (97.4)
Yes	154 (0.8)	143 (0.8)	11 (2.6)

Table 3 (continued)

Maternal Characteristics for Preterm and Term Births Following Spontaneous Labour in Low Risk Nulliparous Women

CHARACTERISTICS	**ALL SPONTANEOUS LABOUR** ***n* = 18,340** *n* (%)	**TERM SPONTANEOUS LABOUR** ***n* = 17,909** *n* (%)	**PRETERM SPONTANEOUS LABOUR** ***n* = 431** *n* (%)
Nutritional Problems			
Gestational weight gain			
Good	18,188 (99.2)	17,761 (99.2)	427 (99.1)
Poor	152 (0.8)	148 (0.8)	4 (0.9)
Anemia			
No	18,279 (99.7)	17,851 (99.7)	428 (99.3)
Yes	61 (0.3)	58 (0.3)	3 (0.7)

*Pearson chi-square significant at $p < 0.05$

Note. Excluded stillbirths, multiple births, births to non-Alberta residents and deliveries associated with either ruptured membranes or iatrogenic (medical) intervention; all definitions for risk factors can be found in Table 2

Table 4

Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Predictors of Spontaneous Preterm Labour in Low Risk Nulliparous Women

CHARACTERISTICS	CRUDE OR (95% CI)	[1]ADJUSTED OR (95% CI)
Demographic		
Maternal age (years)		
20-24	1.22 (0.97, 1.53)	1.13 (0.90, 1.44)
25-29	1.00 Reference	1.00 Reference
30-34	1.27 (0.97, 1.65)	1.27 (0.98, 1.66)
≥ 35	1.71 (1.19, 2.46)*	1.71 (1.19, 2.46)*
Genetic and Constitutional		
Maternal height (cm)		
≥ 152	1.00 Reference	----
< 152	1.25 (0.66, 2.37)	
Maternal pre-pregnancy weight (kg)		
≤ 45	2.14 (0.87, 5.29)	----
46-90	1.00 Reference	
≥ 91	0.88 (0.56, 1.39)	
Lifestyle Factors		
[2]Smoking		
No	1.00 Reference	1.00 Reference
Yes	1.31 (1.05, 1.64)*	1.25 (0.98, 1.58)
Alcohol use		
No	1.00 Reference	----
Yes	1.01 (0.50, 2.05)	
Drug dependency		
No	1.00 Reference	1.00 Reference
Yes	3.25 (1.75, 6.05)*	2.83 (1.50, 5.37)*

Table 4 (continued)

Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Predictors of Spontaneous Preterm Labour in Low Risk Nulliparous Women

CHARACTERISTICS	CRUDE OR (95% CI)	[1]ADJUSTED OR (95% CI)
Nutritional Problems		
Gestational weight gain		
Good	1.00 Reference	----
Poor	1.12 (0.41, 3.05)	
Anemia		
No	1.00 Reference	----
Yes	2.16 (0.67, 6.91)	

OR: odds ratio; 95% CI: 95% confidence interval; all definitions for risk factors can be found in Table 2

*Significant $p < 0.05$

[1] Adjusted for all significant variables in the univariate analysis and smoking; final multivariate logistic regression (MLR) model

[2] Confounder with maternal age 20 to 24 years; included in final MLR model

Table 5

Maternal Characteristics and Reproductive Factors for Preterm and Term Births Following Spontaneous Labour in High Risk Nulliparous Women

CHARACTERISTICS	ALL SPONTANEOUS LABOUR *n* = 30,208 *n* (%)	TERM SPONTANEOUS LABOUR *n* = 29 038 *n* (%)	PRETERM SPONTANEOUS LABOUR *n* = 1,170 *n* (%)
Maternal age (years) (mean ± *SD*)	**26.94 ± 4.71**	**26.92 ± 4.70**	**27.26 ± 5.01**
Demographic			
*Maternal age (years)			
20-24	10,451 (34.6)	10,038 (34.6)	413 (35.3)
25-29	11,178 (37.0)	10,807 (37.2)	371 (31.7)
30-34	6,460 (21.4)	6,182 (21.3)	278 (23.8)
≥ 35	2,119 (7.0)	2,011 (6.9)	108 (9.2)
Genetic and Constitutional			
Maternal height (cm)			
≥ 152	29,540 (97.8)	28,401 (97.8)	1,139 (97.4)
< 152	668 (2.2)	637 (2.2)	31 (2.6)
Maternal pre-pregnancy weight (kg)			
≤ 45	141 (0.5)	133 (0.5)	8 (0.7)
46-90	28,262 (93.6)	27,173 (93.6)	1,089 (93.1)
≥ 91	1,805 (6.0)	1,732 (6.0)	73 (6.2)
Lifestyle Factors			
*Smoking			
No	24,320 (80.5)	23,421 (80.7)	899 (76.8)
Yes	5,888 (19.5)	5,617 (19.3)	271 (23.2)
Alcohol use			
No	29,665 (98.2)	28,513 (98.2)	1,152 (98.5)
Yes	543 (1.8)	525 (1.8)	18 (1.5)
*Drug dependency			
No	29,972 (99.2)	28,823 (99.3)	1,149 (98.2)
Yes	236 (0.8)	215 (0.7)	21 (1.8)

Table 5 (continued)

Maternal Characteristics and Reproductive Factors for Preterm and Term Births Following Spontaneous Labour in High Risk Nulliparous Women

CHARACTERISTICS	ALL SPONTANEOUS LABOUR *n* = 30,208 *n* (%)	TERM SPONTANEOUS LABOUR *n* = 29,038 *n* (%)	PRETERM SPONTANEOUS LABOUR *n* = 1,170 *n* (%)
Nutritional Problems			
Gestational weight gain			
Good	29,904 (99.0)	28,748 (99.0)	1,156 (98.8)
Poor	304 (1.0)	290 (1.0)	14 (1.2)
Anemia			
No	30,051 (99.5)	28,891 (99.5)	1,160 (99.1)
Yes	110 (0.4)	103 (0.4)	7 (0.6)
Missing data	47 (0.2)	44 (0.2)	3 (0.3)
Medical Problems			
*Gestational diabetes			
No	29,656 (98.2)	28,517 (98.2)	1,139 (97.4)
Yes	552 (1.8)	521 (1.8)	31 (2.6)
*Poly/oligohydramnios			
No	30,026 (99.4)	28,883 (99.5)	1,143 (97.7)
Yes	182 (0.6)	155 (0.5)	27 (2.3)
Presence of blood antibodies			
No	30,179 (99.9)	29,011 (99.9)	1,168 (99.8)
Yes	29 (0.1)	27 (0.1)	2 (0.2)
*Presence of an acute medical disorder			
No	30,132 (99.7)	28,969 (99.8)	1,163 (99.4)
Yes	76 (0.3)	69 (0.2)	7 (0.6)

Table 5 (continued)

Maternal Characteristics and Reproductive Factors for Preterm and Term Births Following Spontaneous Labour in High Risk Nulliparous Women

CHARACTERISTICS	ALL SPONTANEOUS LABOUR *n* = 30,208 *n* (%)	TERM SPONTANEOUS LABOUR *n* = 29,038 *n* (%)	PRETERM SPONTANEOUS LABOUR *n* = 1,170 *n* (%)
Current Pregnancy			
*Diagnosis of small-for-gestational age infant			
No	29,683 (98.3)	28,560 (98.4)	1,123 (96.0)
Yes	525 (1.7)	478 (1.6)	47 (4.0)
Diagnosis of large for gestational age infant			
No	29,754 (98.5)	28,600 (98.5)	1,154 (98.6)
Yes	452 (1.5)	436 (1.5)	16 (1.4)
Missing data	2 (0.0)	2 (0.0)	0
*Presence of fetal anomaly			
No	29,915 (99.0)	28,768 (99.1)	1,147 (98.0)
Yes	293 (1.0)	270 (0.9)	23 (2.0)
*Malpresentation			
No	29,264 (96.9)	28,244 (97.3)	1,020 (87.2)
Yes	898 (3.0)	750 (2.6)	148 (12.6)
Missing data	46 (0.2)	44 (0.2)	2 (0.2)
Pregnancy Complications			
*Placenta previa			
No	22,232 (73.6)	21,524 (74.1)	708 (60.5)
Yes	25 (0.1)	8 (0.0)	17 (1.5)
Missing data	7,951 (26.3)	7,506 (25.8)	445 (38.0)

Table 5 (continued)

Maternal Characteristics and Reproductive Factors for Preterm and Term Births Following Spontaneous Labour in High Risk Nulliparous Women

CHARACTERISTICS	ALL SPONTANEOUS LABOUR **$n = 30{,}208$** n (%)	TERM SPONTANEOUS LABOUR **$n = 29{,}038$** n (%)	PRETERM SPONTANEOUS LABOUR **$n = 1{,}170$** n (%)
*Bleeding			
No	28,153 (93.2)	27 214 (93.7)	939 (80.3)
< 20 weeks (wks.) gestational age (GA)	1,219 (4.0)	1,163 (4.0)	56 (4.8)
≥ 20 wks. GA	682 (2.3)	537 (1.8)	145 (12.4)
throughout pregnancy	153 (0.5)	123 (0.4)	30 (2.6)
Missing data	1 (0.0)	1 (0.0)	0
*Pregnancy- induced hypertension			
No	29,327 (97.1)	28,225 (97.2)	1,102 (94.2)
Yes	881 (2.9)	813 (2.8)	68 (5.8)
*Pre-eclampsia/eclampsia			
No	29,951 (99.1)	28,810 (99.2)	1,141 (97.5)
Yes	206 (0.7)	180 (0.6)	26 (2.2)
Missing data	51 (0.2)	48 (0.2)	3 (0.3)

*Pearson chi-square significant at $p < 0.05$

Note. Excluded stillbirths, multiple births, births to non-Alberta residents and deliveries associated with either ruptured membranes or iatrogenic (medical) intervention; all definitions for risk factors can be found in Table 2

Table 6

Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Predictors of Spontaneous Preterm Labour in High Risk Nulliparous Women

CHARACTERISTICS	CRUDE OR (95% CI)	[1]ADJUSTED OR (95% CI)	[2]ADJUSTED OR FINAL MODEL (95% CI)
Demographic			
Maternal age (years)			
20-24	1.20 (1.04, 1.38)*	1.18 (0.97, 1.42)	1.20 (1.00, 1.45)
25-29	1.00 Reference	1.00 Reference	1.00 Reference
30-34	1.31 (1.12, 1.54)*	1.25 (1.02, 1.54)*	1.25 (1.01, 1.56)*
≥ 35	1.56 (1.26, 1.95)*	1.49 (1.12, 1.99)*	1.49 (1.12, 1.99)*
Genetic and Constitutional			
Maternal height (cm)			
≥ 152	1.00 Reference	----	----
< 152	1.21 (0.84, 1.75)		
Maternal pre-pregnancy weight (kg)			
≤ 45	1.50 (0.73, 3.07)	----	----
46-90	1.00 Reference		
≥ 91	1.05 (0.83, 1.34)		
Lifestyle Factors			
Smoking			
No	1.00 Reference	1.00 Reference	----
Yes	1.26 (1.09, 1.44)*	1.15 (0.95, 1.39)	
Alcohol use			
No	1.00 Reference	----	----
Yes	0.85 (0.53, 1.36)		
Drug dependency			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	2.45 (1.56, 3.85)*	2.42 (1.39, 4.22)*	2.62 (1.52, 4.52)*

Table 6 (continued)

Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Predictors of Spontaneous Preterm Labour in High Risk Nulliparous Women

CHARACTERISTICS	CRUDE OR (95% CI)	[1]ADJUSTED OR (95% CI)	[2]ADJUSTED OR FINAL MODEL (95% CI)
Nutritional Problems			
Gestational weight gain			
Good	1.00 Reference	----	----
Poor	1.20 (0.70, 2.06)		
Anemia			
No	1.00 Reference	----	----
Yes	1.69 (0.79, 3.65)		
Medical Problems			
Gestational diabetes			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	1.49 (1.03, 2.15)*	2.04 (1.34, 3.12)*	2.04 (1.34, 3.12)*
Poly/oligohydramnios			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	4.40 (2.91, 6.65)*	3.17 (1.81, 5.56)*	3.23 (1.84, 5.65)*
Presence of blood antibodies			
No	1.00 Reference	----	----
Yes	1.84 (0.44, 7.75)		
Presence of an acute medical disorder			
No	1.00 Reference	1.00 Reference	----
Yes	2.53 (1.16, 5.51)*	1.06 (0.25, 4.48)	
Current Pregnancy			
Diagnosis of small-for-gestational age infant			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	2.50 (1.84, 3.39)*	1.97 (1.30, 2.99)*	2.02 (1.33, 3.05)*

Table 6 (continued)

Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Predictors of Spontaneous Preterm Labour in High Risk Nulliparous Women

CHARACTERISTICS	CRUDE OR (95% CI)	[1]ADJUSTED OR (95% CI)	[2]ADJUSTED OR FINAL MODEL (95% CI)
Diagnosis of large for gestational age infant			
No	1.00 Reference	----	----
Yes	0.91 (0.55, 1.50)		
Presence of fetal anomaly			
No	1.00 Reference	1.00 Reference	----
Yes	2.14 (1.39, 3.28)*	1.71 (0.97, 3.01)	
Malpresentation			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	5.46 (4.53, 6.59)*	5.25 (4.09, 6.74)*	5.32 (4.15, 6.82)*
Pregnancy Complications			
Placenta previa			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	64.60 (27.79, 150.19)*	22.36 (8.63, 57.96)*	22.56 (8.73, 58.30)*
Bleeding			
No	1.00 Reference	1.00 Reference	1.00 Reference
< 20 weeks (wks.) gestational age (GA)	1.40 (1.06, 1.84)*	1.49 (1.06, 2.08)*	1.49 (1.07, 2.08)*
≥ 20 wks. GA	7.83 (6.44, 9.51)*	5.85 (4.43, 7.71)*	5.86 (4.44, 7.73)*
throughout pregnancy	7.07 (4.72, 10.59)*	7.00 (4.28, 11.43)*	7.09 (4.34, 11.57)*
Pregnancy-induced hypertension (PIH)			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	2.14 (1.66, 2.76)*	1.81 (1.20, 2.72)*	1.80 (1.20, 2.70)*

Table 6 (continued)

Crude and Adjusted Odds Ratios and 95% Confidence Intervals for Predictors of Spontaneous Preterm Labour in High Risk Nulliparous Women

CHARACTERISTICS	CRUDE OR (95% CI)	[1]ADJUSTED OR (95% CI)	[2]ADJUSTED OR FINAL MODEL (95% CI)
[3]Pre-eclampsia/ eclampsia			
No	1.00 Reference	1.00 Reference	1.00 Reference
Yes	3.65 (2.41, 5.53)*	1.77 (0.90, 3.51)	1.76 (0.89, 3.49)

OR: odds ratio; 95% CI: 95% confidence interval; all definitions for risk factors can be found in Table 2

*Significant $p < 0.05$

[1] Adjusted for all significant variables in the univariate analysis (Stage 1 of multivariate logistic regression)

[2] Adjusted for all significant variables after Stage 1 and pre-eclampsia/eclampsia; final multivariate logistic regression (MLR) model

[3] Confounder with PIH; included in the final MLR model

CHAPTER 5 – DISCUSSION

The question of whether older maternal age (≥ 35 years at time of delivery) increases the risk of spontaneous preterm labour is an important one to answer due to the increasing number of women delaying the birth of the first child until their mid-thirties and beyond, the increasing use of assisted reproductive technologies, and the concurrent rise in preterm birth rates, despite improvements in high risk obstetrical care and neonatal medicine.

The objectives of this study were: 1) to determine if older maternal age at first birth was an independent risk factor for spontaneous preterm labour (defined as spontaneous labour leading to delivery at < 37 completed weeks gestation that is not associated with either ruptured membranes or iatrogenic intervention) (Ananth et al., 2005) or a risk marker that exerts its influence indirectly through other age-dependent risk factors; and 2) to establish separate risk models for healthy nulliparous women with no pregnancy complications (low risk) and healthy nulliparous women who developed one or more pregnancy complications (high risk).

The findings from this study indicate that after controlling for age-dependent and other potential confounders, older maternal age does increase a woman's chance of developing spontaneous preterm labour, regardless of whether the woman remains healthy throughout pregnancy or whether the woman develops one or more pregnancy complications. For healthy nulliparous women who do not develop pregnancy complications, the risk of spontaneous preterm labour increases at 35 years of age and older. For healthy nulliparous women who develop one or more pregnancy complications, the risk of spontaneous preterm labour increases at 30 years of age and older.

After controlling for smoking and drug dependency, it was determined that older nulliparous women (women ≥ 35 years of age) who remained healthy throughout pregnancy (low risk) were almost 2 times more likely to deliver a preterm infant following spontaneous labour than women 25 to 29 years of age (reference group). These women were also 3 times more likely to experience spontaneous preterm labour if they were drug dependent during pregnancy. Drug dependent women had the greatest risk of delivering a preterm infant following spontaneous labour.

For healthy nulliparous women who developed one or more pregnancy complications (high risk), the findings showed that older maternal age had a direct and independent impact on spontaneous preterm labour. Moreover, a dose-response relationship was found beginning at 30 years of age (i.e., the risk of spontaneous preterm labour increased slightly with advancing maternal age). Women 30 to 34 years of age were 1.3 times more likely to develop spontaneous preterm labour and women 35 years of age an older were 1.5 times more likely to develop spontaneous preterm labour, even after controlling for several age-dependent confounders, including pregnancy complications.

Spontaneous preterm labour was also more likely to occur for high risk nulliparous women who were drug dependent during pregnancy, for women who had gestational diabetes, for women with poly/oligohydramnios, for women who were diagnosed with a SGA infant, for women diagnosed with a fetal malpresentation, and for women who developed pregnancy complications (i.e., bleeding during pregnancy, placenta previa, PIH). The greatest risk of spontaneous preterm labour occurred among women with bleeding throughout pregnancy and among women diagnosed with placenta previa. Bleeding throughout pregnancy was associated with a 7-fold increase and placenta previa was associated with a 23-fold increase in a woman's chance of developing spontaneous preterm labour. Fetal malpresentation was not considered to be a predictive or a causal variable for spontaneous preterm labour: fetal malpresentation may possibly have occurred as a result of spontaneous preterm labour, and how the small preterm infant became positioned in the birth canal.

Previous researchers have identified pregnancy complications as intermediate outcomes of preterm birth (i.e., other risk factors can affect preterm birth by exerting their influence indirectly through pregnancy complications) (Lang et al., 1996). In addition, pregnancy complications are considered to be age-dependent confounders because there is an increased risk of pregnancy complications in women of older maternal age (Berkowitz et al., 1990; Gilbert et al., 1999; Jolly et al., 2000; Prysak et al., 1995; Salihu et al., 2003). Therefore, in this study, each pregnancy complication was entered separately towards the end of the risk model for high risk women to determine if older maternal age indirectly influenced spontaneous preterm labour through its effect on a specific pregnancy complication. Although there was a slight decrease in the odds ratio for older maternal age when placenta previa was entered into the regression model, older maternal age remained a significant independent predictor of spontaneous preterm labour.

In the past, researchers have mainly focused on studying the etiologic pathways for PT-both (i.e., preterm birth preceded by preterm premature rupture of membranes or spontaneous labour) (see Table 1). In this study, the dependent variable (outcome of interest) was spontaneous preterm labour. The only researchers in Table 1 to develop risk models for spontaneous preterm labour were Berkowitz et al. (1998) and Harlow et al. (1996). Therefore, the results of this study can only be compared to the results of these two studies.

Similar to the current study, Harlow et al. (1996) examined the risk factors for spontaneous preterm labour among healthy women. They found that maternal age (per 5 years) was not a significant predictor of spontaneous preterm labour; however, maternal age was not the primary focus of their study. Instead, maternal age was controlled in the risk modeling. The result for maternal age differs from the findings in the current study. Possible explanations for the observed differences could be the following: 1) Harlow et al. did not develop separate risk models for healthy nulliparous versus healthy multiparous women (i.e., both nulliparous and multiparous women were included in the same model); and 2) these researchers did not include pregnancy complications in their model. In order to determine the direct and independent effect of older maternal age on spontaneous preterm labour, it is necessary to control for age-dependent confounders in the risk modeling.

Regarding the first explanation, researchers have concluded that investigators examining the impact of older maternal age on adverse pregnancy outcomes must acknowledge that women who delay childbearing are not a homogeneous group. Therefore, investigators must incorporate the heterogeneity of the maternal population into their study design (Newburn-Cook & Onyskiw, 2005). Researchers examining the influence of older maternal age on preterm delivery following spontaneous labour need to stratify the study population by parity and develop separate risk models for nulliparous and multiparous women.

There may be a differential effect of older maternal age on spontaneous preterm labour for different groups of women, specifically nulliparous versus multiparous women. If this was the case, the inclusion of both nulliparous and multiparous women in the study by Harlow et al. may have resulted in the masking of an association between maternal age and spontaneous preterm labour in these groups of women, and subsequently biased the odds ratio towards 1 (no association between advancing maternal age and spontaneous preterm labour).

In the study by Berkowitz et al. (1998), it was reported that there was no increased risk of spontaneous preterm labour among women of older maternal age, which is not supported by the findings in this study. Once again, the discrepancy in findings may possibly be due to methodological differences. Like Harlow et al. (1996), Berkowitz and her colleagues included both multiparous and nulliparous women in their hospital-based study to investigate the effects of several risk factors on the occurrence of each preterm birth subtype. These researchers also included women with pre-existing medical conditions in their study population. Pre-existing medical conditions are considered to be age-dependent confounders.

Hospital-based studies may be subject to selection biases resulting from the different referral patterns and the types of patients receiving care. For example, the study population in the Berkowitz et al. study may have had a different age distribution when compared the entire population of women giving birth and their hospital-based sample may have had a higher incidence of pre-existing medical problems and pregnancy complications (a high risk population that would differ from the high risk population in this study). It must be remembered that the current population-based study, which is less susceptible to selection bias, included only healthy nulliparous women (women with pre-existing chronic medical illnesses were not included in the risk modeling). These methodological differences may provide some explanation for the differences in results.

As noted previously, Berkowitz et al. (1998) included women with pre-existing medical conditions in their study population. Women with pre-existing medical conditions are more likely to be at risk for pregnancy complications and, therefore, are at a greater risk for early delivery. By controlling for these additional age-dependent confounders in the risk modeling, older maternal age may have been a risk marker in this patient population, acting indirectly through these medical conditions and/or pregnancy complications to influence spontaneous preterm labour.

Contrary to the results of previous studies, this study showed that there is a significant association between older maternal age and the risk of spontaneous preterm labour among nulliparous women who remain healthy throughout pregnancy (low risk) and among healthy nulliparous women who develop one or more pregnancy complications (high risk). These results are valid for the study population defined because of the methodology used to examine the effect of older maternal age on the incidence of spontaneous preterm labour. This is the first population-based study to specifically investigate if older maternal age acts directly or indirectly on the risk of spontaneous preterm labour. It is also the first study to have two different risk models (i.e., one for low risk and one for high risk nulliparous women) where the heterogeneity of the maternal population is considered, as well as the heterogeneity of preterm birth (i.e., there may be different etiological pathways for spontaneous preterm labour, preterm births arising from preterm PROM, and medically indicated preterm births).

Study Strengths and Limitations

There were several methodological strengths present in this study. First, the study was a population-based cohort study that included all births occurring in hospitals and at home (home births attended by registered midwives) in Northern and Central Alberta. Therefore, the potential problem of selection bias was minimized. Second, several age-dependent confounders, as well as other potential confounders and interactions were simultaneously controlled for in the risk modeling using multivariate logistic regression. This was possible because there was adequate study power present resulting from the relatively large sample size and the use of the provincial perinatal data. Third, recall bias was not an issue in this study. Potential risk factors used in the risk modeling were collected on admission to hospital and during labour, before the birth outcome was known.

One of the main strengths of this study was the ability to separate preterm birth into its three subtypes. In the past, the majority of researchers have clustered preterm births preceded by spontaneous labour or preterm premature rupture of membranes (PROM) into a single birth outcome (referred to as PT-both in this study), as can be seen in Table 1. Preterm births are classified into three distinct clinical presentations (or subtypes): those that arise from spontaneous preterm labour, those that arise from preterm PROM, and those that are medically indicated. As a result, there may be differential effects that older maternal age has on the varying pathways leading to preterm delivery. In this study, the type of labour (i.e., spontaneous or preterm PROM) and medical indications for early delivery were all recorded in the Alberta Perinatal Health Program (APHP) North Perinatal database. Therefore, preterm births were separated into the three different subtypes and the impact of older maternal age on one specific etiologic pathway, spontaneous preterm labour, was estimated.

Researchers have stressed that the heterogeneity of the maternal population needs to be considered when the impact of older maternal age on preterm birth is examined because the effects of age may vary for different groups of women (Newburn-Cook & Onyskiw, 2005). In this study, several factors that differ among pregnant women were incorporated into the study design. Multiparous women and women with pre-exiting chronic medical conditions were both excluded from the study population. Furthermore, the study population was stratified into healthy women who did not develop pregnancy complications and healthy women who developed one or more pregnancy complications. As a result, two separate etiologic pathways were examined for healthy nulliparous women and any confounding effects from parity and pre-existing chronic illnesses were eliminated.

Multiparous women have different issues to contend with than nulliparous women. For example, having other children to look after at home will lead to different challenges in the day to day activities of multiparous women. In addition, multiparous women may be delivering their children at an older age when compared to nulliparous women, they may be more likely to have used assisted reproductive technologies/ovulation drugs due to difficulties conceiving or a history of infertility (C.V. Newburn-Cook, personal communication, August 11, 2006), and they may have a previous obstetrical history that puts them at an additional risk for spontaneous preterm labour (e.g., previous preterm birth) (Berkowitz et al., 1998; Harlow et al., 1996). Given the differences between nulliparous and multiparous women, including only a nulliparous sample in this study was a definite strength.

Another strength of this study was the completeness of the risk factor data included in the risk modeling. Missing data for the nulliparous women included in this study was negligible. There was no missing data for healthy low risk nulliparous women. For healthy high risk women, the missing data for anemia (0.2%), malpresentation (0.2%), and pre-eclampsia/eclampsia (0.2%) was minimal.

Several precautions are taken routinely by the APHP to ensure both completeness and accuracy of the data entered into the APHP North Perinatal Database. After data entry, a validation procedure is implemented. A crosscheck of the manual tabulation of key variables with an electronic tabulation of these same variables takes place on a monthly basis. A minimum of 1 in 20 records is verified with the data entry to ensure accuracy. Hospitals that submit data electronically to the APHP also validate their own data prior to submission. In addition, the APHP completes a validation process for all data submitted electronically. Because of the validation checks in place, the misclassification of exposure variables was reduced.

There were also study limitations. The misclassification of spontaneous preterm labour may have been a possibility for cases where the estimation of gestational age was based on the date of last menstrual period and this date was not confirmed by ultrasound. However, the misclassification of spontaneous preterm labour was likely negligible in this study because fetal ultrasound is widely available throughout Alberta and was available prior to the study period. Moreover, any misclassification of spontaneous preterm labour would have led to an underestimation of the odds ratios, so the results of this study would still be valid (Newburn-Cook et al., 2002).

One of the main limitations in this study was the problem inherent with using an administrative database. The risk modeling was limited to the maternal and reproductive variables recorded in the APHP North Perinatal Database and the way in which these risk factors were aggregated. Consequently, only a partial risk model could be developed. For example, there was no information on antenatal care, race, socioeconomic status (education, occupation, income, marital status), or abruptio placentae, variables that have been identified in the literature reviewed as potential risk factors for spontaneous preterm labour (Berkowitz, 1985; Berkowitz et al., 1998; Harlow et al., 1996; Heaman et al., 2005; Kramer et al., 1992; Lang et al., 1996; Mercer et al, 1996). Psychological (e.g., stress) or environmental factors were also not captured in the database. Furthermore, the confounding effects of acute medical disorders could not be assessed for high risk women in the multivariate logistic regression because this category included several disorders (e.g., urinary tract infection, acute asthma, thyrotoxicosis) that were not mutually exclusive.

Implications for Nursing

The results from this study suggest that appropriate information regarding the risks of postponing childbirth is needed long before women decide to have a family. Nulliparous women in their mid-thirties and older are at higher risk for delivering a preterm infant following spontaneous labour than women who deliver at a younger age, regardless of whether they are healthy prior to or throughout pregnancy. For some women (i.e., nulliparous women who develop one or more pregnancy complications) the risk of spontaneous preterm labour begins at 30 years of age.

Nurses can play a key role, in conjunction with physicians and other community agencies, in educating women about the risks associated with delaying childbirth. Supermarkets, television, community publications, and family physician practices are only some of the venues that can be used for delivering appropriate health information to women regarding the potential risks of spontaneous preterm labour. In addition, more women today are using the Internet as a source of health information. Nurses should work with their professional associations to ensure that valid research results regarding the risks associated with delayed childbearing are distributed online. Having accurate information pre-conceptually can help women make informed choices about when to start a family.

Nurses can help to minimize the possibility of spontaneous preterm labour by encouraging women to seek early prenatal care. Because women of older maternal age are at an increased risk for pregnancy complications, care by a skilled practitioner is necessary to ensure that any interventions required to help prevent spontaneous preterm labour are implemented in a timely manner. Nurses can participate in monitoring and providing early treatment for medical problems and complications that arise during pregnancy.

Implications for Future Research

Although in this study an association between older maternal age and spontaneous preterm labour among low risk and high risk women was found, more research is required to examine if this increased risk exists for preterm birth arising from preterm premature rupture of membranes (PROM) or medically indicated preterm births. In order to determine where the "at risk" age begins for these birth outcomes, investigators should include a narrowly defined set of maternal age categories (e.g., < 15, 15 to 17, 18 to 19, 10 to 24, 25 to 29, 30 to 34, 35 to 39, ≥ 40 years), or they should empirically determine where the age cutoffs are that show an increased risk to mother and fetus (Newburn-Cook & Onyskiw, 2005). This will help health professionals to identify where the "at risk" age begins for preterm birth arising from preterm PROM or medical intervention and, therefore, appropriate pre-conceptual or prenatal counseling regarding the risks for preterm birth can take place.

Previous researchers investigating the etiologic pathways for spontaneous preterm labour have arbitrarily chosen a reference group for maternal age (see Table 1). Several of these investigators included a reference group with a wider age gap (e.g., 19 to 35 years in Heaman et al., 2005 and 25 to 34 years in Lang et al., 1996). In this study, the age group 25 to 29 years was empirically chosen as the optimal age for reproduction (i.e., reference group). Furthermore, it was demonstrated that the risk for spontaneous preterm labour actually began for high risk nulliparous women at age 30 to 34 years. If women 30 to 34 years of age were included in the reference group in this study, the odds ratio for maternal age would have been biased towards 1 and a significant association for older maternal age would not have been identified. Investigators need to pay attention to their definition of the optimal age for reproduction if the effects of maternal age on pregnancy outcomes (e.g., preterm PROM or medically indicated deliveries) are to be estimated.

To determine the direct or indirect effect of maternal age on pregnancy outcomes, future investigators need to continue examining other groups of women than the ones identified in this study. The reasons for postponing childbirth are not homogenous. Some women voluntarily delay starting a family, some start second families with a new spouse, some may have a history of infertility, and some may delay for other reasons (Newburn-Cook & Onyskiw, 2005). All these varying reasons could influence the effect of maternal age on preterm birth. In addition, the presence of pre-existing chronic illness, the use of assisted reproductive technologies, differences in socioeconomic status, and multiparity may also play a role in how maternal age effects birth outcomes and should be considered in future risk modeling.

Because only a partial risk model could be provided in this study, more research is needed to investigate the effects of other risk factors on the risk of each preterm birth subtype. The potential role these risk factors play in mediating the effect of older maternal age should also be investigated. For example, women who choose to delay childbearing are often better educated, more psychologically ready for pregnancy and more socially advantaged, which all contribute to more positive pregnancy outcomes (Chen & Millar, 2000; Freeman-Wang & Beski, 2002; Lansac, 1995; Mansfield & McCool, 1989; Newburn-Cook & Onyskiw, 2005). Therefore, the effect of socioeconomic status and psychological factors (e.g., stress) on the risk of each preterm birth subtype should be assessed. In particular, the mediating role that these factors may have on the impact of maternal age should be examined. The effect of antenatal care and race should also be considered in future studies examining the influence of older maternal age on each preterm birth subtype.

Conclusion

The results of this study demonstrate that older maternal age increases the risk of spontaneous preterm labour regardless of whether nulliparous women remain healthy throughout pregnancy or whether they develop pregnancy complications. Furthermore, the findings indicate that the risk for spontaneous preterm labour begins at 30 years of age as opposed to 35 years of age for healthy nulliparous women who develop one or more pregnancy complications.

Women are looking to health professionals and searching online for accurate information on the risks surrounding adverse birth outcomes. The results of this study suggest that women should be informed early on about the increased risk for spontaneous preterm labour when childbearing is postponed. Nurses are in a key position to provide the appropriate information regarding the risks of delaying childbirth because of their presence in a variety of health care settings. Nurses should work together with other health care professionals to provide pre-conceptual counseling for women on the risks associated with spontaneous preterm labour. In addition, nurses should work with their professional associations to help ensure that accurate information is disseminated through the Internet.

Older pregnant women should be encouraged to seek early prenatal care due to their increased risk of pregnancy complications. Appropriate medical surveillance can help ensure that any necessary treatment is provided in a timely fashion if medical problems and pregnancy complications arise. In turn, the incidence of spontaneous preterm labour can be decreased and the health outcomes for infants can be improved.

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